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PELLAGRA AND SOME OF ITS PROBLEMS.[1]

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Extended research on the part of scientific men, physicians and others, in the several countries of Europe where pellagra has long prevailed, has resulted in the production of a literature that is as vast as it is illuminating. The relatively recent appearance of the disease on this side of the Atlantic has awakened a special interest in the subject, not merely among American observers, but also among authorities, both Italian and English, who have learned with no little surprise of the new chapter to be written in this century on the history of the disorder. In the limits of the present paper only the briefest reference can be made to the labors

[1] The record of neurological symptoms in the patients described in this paper was made by Peter Bassoe, M.D., assistant professor of nervous and mental diseases in the Rush Medical College; and the record of blood-findings, including the bacteriology in nine patients, was made by D. J. Davis, M.D., instructor in pathology and medicine in Rush Medical College. The author is greatly indebted to these gentlemen for these reports, and desires to express his thanks to Dr. J. W. Babcock, physician and superintendent of the State Hospital for the Insane, Columbia, South Carolina, for the privilege of examining pellagra patients, both public and private, during the session of the National Pellagra Conference held in that city on November 3 and 4, 1909; and unites with his collaborators in acknowledging obligations to Dr. George A. Zeller and Dr. George Michell, of the Peoria State Hospital for the Insane, Bartonville, Illinois, for permission to observe and make special study of pellagrous patients in that institution; also to Dr. V. H. Podstata, superintendent and physician of the Hospital for the Insane at Elgin, Illinois; and to Dr. L. J. Pollock, physician of the Cook County, Illinois, Asylum for the Insane, for the opportunity of making examination of other pellagrous patients in these institutions.

of the authors whose names have been identified with the study of the malady. The attempt is here made briefly to sketch, as far as may be, the phenomena of the disease as they have been recognized in this country, and incidentally to formulate some of the problems with which the students of pellagra in the United States apparently are confronted.

Many of the several names which have been given to the disease reflect the opinions once prevalent respecting its nature and cause. It has been termed Mal de la Rosa, Risipola Lombarda, Lombardy Erysipelas, Lepra Italica, Alpine Scurvy, Mal Rosso, Mal Roxo, Maïdica, Psychoneurosis Maïdica, Maladie de la Teste, Malattie della Miseria, Mal de Sole, Mal de Asturias, Raphania Maïstica, Malattia dell' Insolato di Primavera; and other titles have been employed in its designation. Though vaguely recognized before his time, the first authentic description of the disease was made by a Spanish physician, Gaspar Casal, under the title Mal de la Rosa, the fruit of observation made by him among the peasants of the Asturias in the year 1735. His work was written in the Latin tongue, and published after his death by Joseph Garcia in the year 1762. In this monograph the portrait (Fig. 1) illustrating the localization of the disease correctly represents its cutaneous stigmas as they are betrayed today. His description of the pellagrous skin is noticeably accurate: "Degenerat tandem in crustam siccissimam, scabrosam, nigricantem, profundis sæpissime intercissam fissuris, etc."

Frapolli, of Milan, in 1771, is commonly reported as first to have given the name to the disease by which today it is most generally known, but in fact he merely reproduced a title current among the people of his day: "Morbus, vulgo, Pellagra." In the long list of authors who followed, from Strambio, Marzari, Alibert, Rayer, and Raymond, to Lombroso, Sandwith, Babes and Sion, and Sir Patrick Manson, can be traced the progress of the disease in Europe from Spain to Southern France, northern and central Italy, Corfu, upper Egypt, and other parts of Africa, Austria, Servia, Bulgaria, Roumania, Asia Minor, India, Mexico, Barbadoes, and portions of North and South America.

The prevalence of the disorder in Europe may be estimated to a degree from its ravages in Italy, which has suffered more than any one other country. In Lombardy alone from the year 1770, when attention was first paid to the serious character of the endemic, to the year 1880 the number of pellagrins increased from 20,000 to 104,067. It has been estimated that in a population of 16,689,735, of northern and central Italy, the proportion of those affected with the disease rose from one in sixty to one in nineteen of the inhabitants. At the present time, thanks to the extraordinary efforts of the Government in the matter of improving the hygienic and especially the dietetic habits of the peasantry, a marked decrease

FIG. 1.—Casal's illustration of cutaneous lesions in pellagra.

has been accomplished in the number of fresh cases of the disease; and in a few districts where there was a readiness to conform to the regulations provided by the State, it is reported that pellagra has been practically eradicated.

The great multiformity in the symptoms displayed in different cases, and the obvious influence of the rays of solar light in the production of certain of the cutaneous phenomena, have led several authors to an opinion, formulated by Winternitz in 1876, that there is not a nosological entity which corresponds to the term pellagra. Bonnet, four years later, and other writers, descanting upon supposed cases of "pseudopellagra," lean to the same conclusion, a conclusion which seems to have been shared by several modern observers, and which gave weight to the French aphorism that pellagrins are "*des malades sans une maladie.*" Reference is made to this opinion chiefly with a view to emphasizing the fact that pellagra, as its phenomena have been unfolded before the clinicians of our day, is a disorder of admitted contradictions, of complexity of morbid symptoms, of strange subversions of any determinate order of evolution. Yet, all said and done, a conscientious study of the disease leads to the conviction that pellagra, in its complexus of symptoms, is a distinct affection, resembling none other, and, despite irregularity in the order of its manifestations impressed with a definite and characteristic physiognomy. Its poison, though as yet unrecognized, is probably one; the effects of that poison, operating upon a wide field of the human economy, wider than in most of the serious endemic maladies of the human family, are many.

Pellagra is neither infectious, contagious, nor inherited. In countries where labor in the fields is accomplished chiefly by men, these suffer more than women. Elsewhere, the subjects of the disease are in larger proportion women. The one chief predisposing factor in its production is, without question, the asthenic condition of a poverty-stricken, poorly nourished, and enfeebled class of subjects. Though not inherited, pellagra may affect children at an early age; the larger number of patients, however, develop its symptoms between the close of the second and of the fifth decade of life. That it is a disorder chiefly developed in warm countries can scarcely be doubted apart from the arguments adduced in favor of its close connection with the crops raised within certain fixed geographical limits. The southern portions of Europe have unmistakably suffered more than those in the extreme north. The probable geographical limits lie between 40° and 50° north latitude.

The effects of pellagrous intoxication of the human body are exerted chiefly in three systems of the economy—the nervous, the cutaneous, and the gastro-intestinal. The order and importance of these is not exactly determined. Examining the three from different points of view, authors have attributed sometimes to one

of these and again to another a chief importance. But the cutaneous symptoms have not only given to pellagra its most commonly employed designation (Ital., *pelle*, skin; *agra*, rough), but, further, have furnished its most constant and determinate features. It is possible that there may be a *pellagra sine pellagra*, but few clinicians would venture to make a diagnosis of this sort in any sporadic case beyond the limits of a pellagrous district.

The classical type of pellagra recognized in Europe may be briefly described as follows (the American variations from the Italian and Egyptian portraits will be noticed in passing):

The question of a distinct prodromal period introduces at once to the confusion which has prevailed respecting many features of the disorder. By some it is believed that year after year, before the first unmistakable symptoms are betrayed, the patient experiences an increasing sensation of languor and of general malaise. It is clear, however, that even in the class of subjects who tolerate minor ailments with relative equanimity, in the early spring season of the year there is experienced an unwonted lassitude, vertigo, epigastric pain, bowel looseness, and inappetence. Often there is coincident involvement of the tongue, which may be coated, or become reddened and studded with prominent papillæ. More rarely there are superficial losses of its enveloping membrane, and in extreme cases, ulceration of the mucosa. Other uncomfortable symptoms experienced at this period are more or less severe headache, accompanied by vomiting. Pellagra has been described as a feverless disease. The temperature throughout may be normal. Again, by one of those odd anomalies which frequently are to be recognized in the course of the disease, all the gastro-intestinal symptoms may be ameliorated at the date of the onset of the cutaneous efflorescence. As the eruptive phenomena are practically alike in patients affected with pellagra on both sides of the Atlantic, the following may be held to be fairly descriptive of the average of cases, wherever observed. For the convenience of classification of symptoms, three stages are described by writers.

The eruption (pellagrous erythema) in the first stage develops, as a rule, suddenly and with practical symmetry, in the days of early spring, and is commonly limited to the uncovered parts of the body exposed to the sun's rays (the face, neck, hands, and, in those not clothing the lower limbs, also the feet). The entire face may be symmetrically involved, producing thus the pellagrous "mask" (Fig. 2). Often, however, portions only of the face are involved; the brow may be spared in men who wear hats; while in insane women, whose faces are less protected, we have seen characteristic "welts" across the upper portion of the forehead. In both sexes it is not rare to see the beardless chin involved; occasionally the cheeks also, to the exclusion of other parts.

The erythematous circlet about the neck (Ger., *Casal'sche*

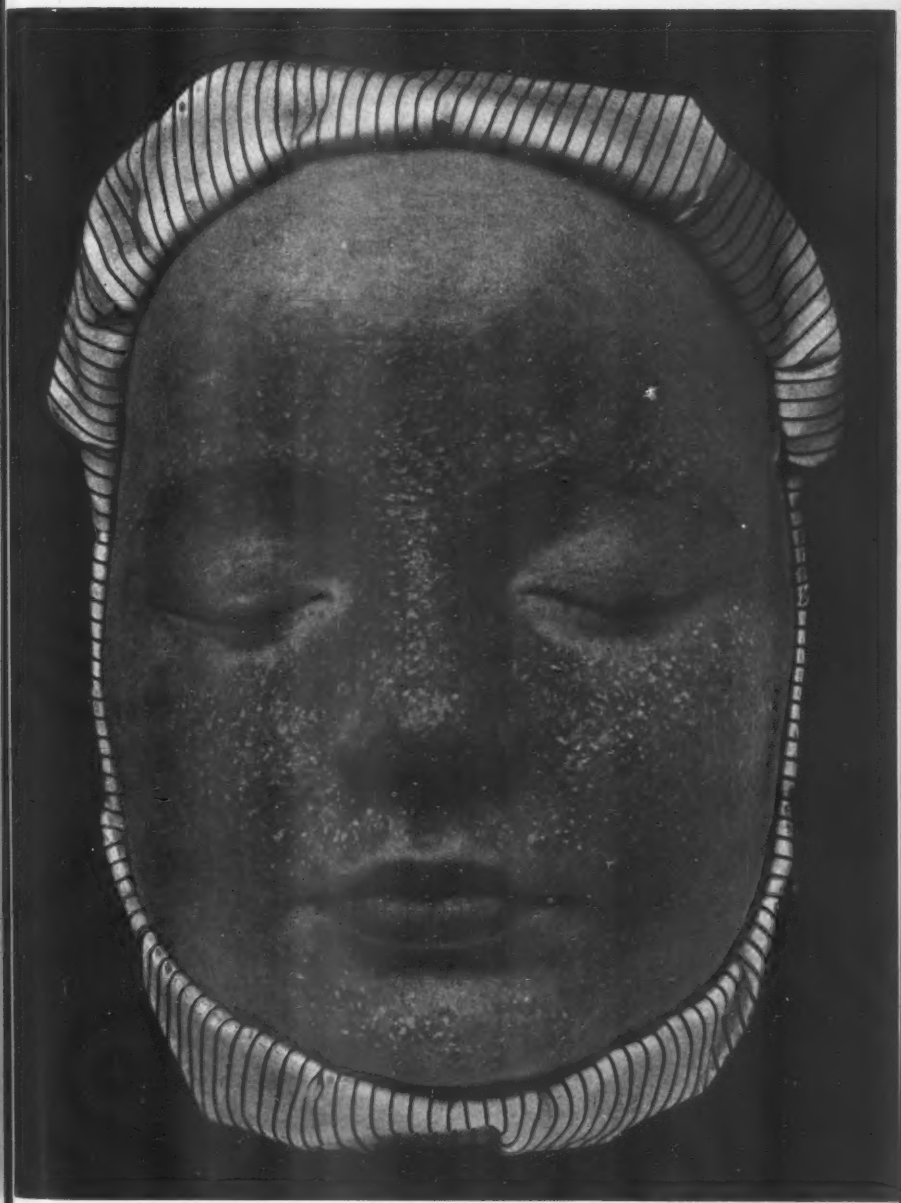

FIG. 2.—Pellagrous "mask" of the face. (Reproduced through the courtesy of Prof. Ludwig Merk, of Innsbruck.)

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Halsband; Ital., *Il collare pellagroso*), first depicted by Casal, is one of the characteristic stigmas of the disease. In front, distinct lines of demarcation can usually be recognized at the lower border of the "collar," representing the line of contact of the shirt or other garment protecting the inferior part of the neck. The upper border of the "collar" in front is often as distinctly outlined by reason of the protection from sunlight furnished by the chin. Behind, the "collar" stretches from the clothing below to the line of the hairs of the occiput. The ears may be simultaneously affected.

FIG. 3.—Pellagrous erythema of the hands. Patient not insane. (Courtesy of Dr. Michell.)

The dorsa of the hands present probably the most common and the most vivid of the cutaneous expressions of the disease. They are, as also the other affected surfaces, usually symmetrically involved, the eruptive symptoms when fully developed spreading evenly from the radial to the ulnar side of the hands, sparing the palms and nails (Fig. 3). In but a few cases, those seen by us in the South, have the palms been invaded by extension from the back of the hands. Raymond asserted categorically that the dorsum of the distal phalanx is never attacked, and this even when the region named has not been protected by the position assumed in grasping tools employed by the laborer in the open fields. These statements, however, have been negatived by numerous observations in every large experience.

Dr. Watson points to a characteristic extension of the pellagrous eruption on the hands to the flexor surface, beginning on the radial border, and reaching toward the ulnar by an oblique line forming an irregularly outlined triangular patch, its base at the radius, its apex near the ulnocarpal articulation.

The dorsa of the feet, when exposed equally with the hands,

are similarly affected. The eruption covers the area from the distal phalanges of the toes to the malleoli, as a rule, sparing the heel.

In exceptional cases, departures from the type are striking. The "pellagrous boot" we have seen chiefly in Southern patients; the eruptive symptoms spreading somewhat unevenly from the foot to the upper third of the leg, displayed, as a rule, more abundantly in front than behind. In many cases we have seen distinct

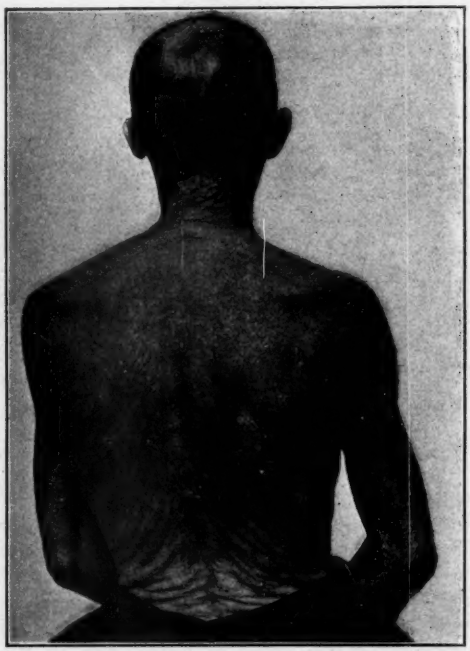

FIG. 4.—Pellagrous erythema, universal. (Courtesy of Dr. Miller.)

involvement of the knees when the legs were scarcely invaded The same is true of the upper extremities, the entire forearm becoming the seat of the eruption, with distinct limitation to the region exposed to the light, showing a line of demarcation at the wrist, the elbows being very distinctly involved, with circumscribed borders. Again, tongue-shaped prolongations may spread from the elbows downward as far as the middle of the forearm. Where the clothing worn by the day laborer has a V-shaped opening in front and behind (as is seen in some of the Egyptian sufferers),

there is a corresponding localization of the eruption, the erythema spreading downward in a triangular patch, its base above both in front and behind. Similarly produced are the irregular areas of involved skin occasionally perceptible over one or both shoulders. The genital region in both sexes is at times attacked, notably the scrotum in men and, more often, the vulva in women. Miller has reported an instance of pellagra universalis (Fig. 4). Cases have been recorded, however, in which, after the exposure of the entirely nude body, the face, hands, and feet only have been involved (Neusser).

The hue of the exanthem differs according to the color scheme of the subject and the length of time during which it has existed. At first the color is a dull red, which has been likened to the appearance of the skin after a common sunburn; yet it is rare that the pinkish hue produced by the rays of the sun in the skin of a blond subject is precisely imitated. The pellagrous erythema at the outset, generally fading temporarily under pressure, is more reddish than pinkish, displayed at times with discrete macules which speedily fuse and produce, on the backs of the hands, for example, a uniformly smooth, reddened, and distinctly outlined area, suggesting, when the cuffs have definitely limited the efflorescence above, the appearance of a glove covering the back of the hand. In the milder cases the macular lesions may fade without producing the "mask" effect; more commonly the eruption persists to a complete involvement of the areas exposed to the light. As the evolution of the erythema advances, the color deepens, refuses to disappear under pressure, and at its height attains a reddish-brown, chocolate, or plum-colored shade, described as "livid bluish," a tint at times suggesting that of sepia. The first eruptive symptoms may disappear in a fortnight with epidermic exfoliation in light flakes, leaving behind a pigmentation differing according to the severity of the precedent engorgement.

The skin thus affected is tense, swollen, and the seat of burning rather than of pruritic sensations. The surface is very rarely scratched. In the dark races, especially the negro, the color of the eruption may take on a grayish hue, with deepening of the normal pigment of the part.

Cases exhibiting vesicular and bullous lesions, in both the northern and southern portions of this country, are popularly termed "wet" (Fig. 5), as contrasted with the "dry" form described above. In these instances vesicles and blebs develop, often with large elevations of the epidermis over chambered sero-pus, followed by desiccation, crusting, and rhagades. These are decidedly the rarer exhibitions of the exanthem, and are believed to be concomitants of the most serious phases of the systemic disorder.

In most of the first attacks the eruptive phenomena fade in a fortnight, leaving the skin pigmented, roughened, and, in the case

of many of the poorer class not under hygienic management, begrimed with dirt.

Many, indeed, of the American patients have a recrudescence of the exanthem in the autumn, some under our observation suffering even from repeated attacks in one season; while the type cases of Italian writers undergo a relighting of the morbid process in the

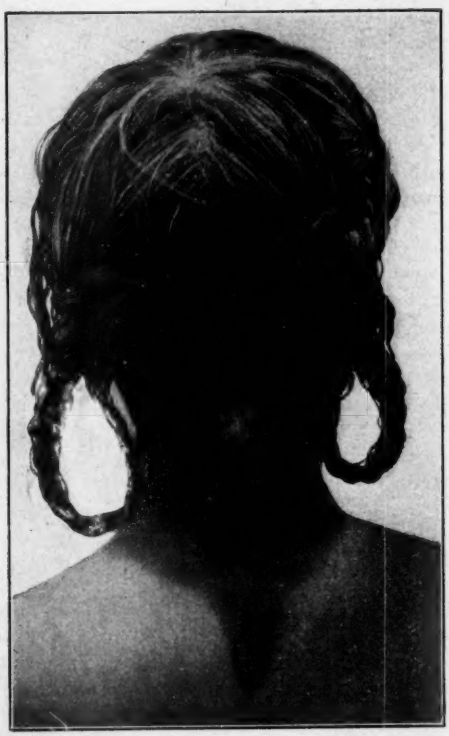

FIG. 5.—Pellagrous erythema of the neck, moist type. (Courtesy of Dr. Zeller.)

skin, only at the succeeding season of spring (second stage), when possibly, without the production of as vivid an exanthem as at the first, the skin again becomes dull reddish in hue, is more deeply infiltrated, and, when the exacerbation passes, in cases in which the hands are involved, leaves these organs covered with a seamed, corded, rugous, and irregularly roughened epidermis, which has given pellagra its distinctive title.

In cases in which a vesico-bullous efflorescence occurs, the picture presented on the back of the hands, after bursting and crusting

FIG. 7.—Atrophy of the skin of the back of the hand succeeding pellagrous erythema. (Reproduced through the courtesy of Prof. Ludwig Merk, of Innsbruck.)

have been accomplished, is that of the skin which has been the seat of artificial vesication (Fig. 6). A granulating surface where the epiderm has been removed becomes covered with a new and tender horny layer, which presents itself with limits furnished by the ragged, partly adherent, and slightly loosened fringes of dirt-colored skin. In cases in which no fluid has been effused, the affected surface scales in larger or smaller flakes of loosened epithelium. After one or more attacks of pellagrous erythema, the skin atrophies, leaving in the site of the exanthem a thinned, cicatriform, parchment-like integument, this last often irregularly altered, the thinning

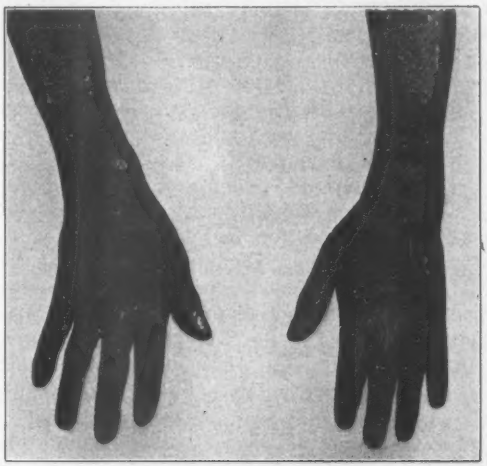

FIG. 6.—Pellagrous erythema of the hands, bullous type. (Courtesy of Dr. Zeller.)

showing occasionally in striæ parallel with the long axis of the hand, rarely as a definitely bordered scar, such as follows ulceration of the integument (Fig. 7).

In severe cases, however (one such was shown us in Columbia), after the onset of the exanthem, ulceration occurs on the backs of the hands. In a few of these the sheaths of the tendons have been exposed. When recovery has ensued, the scarring has not resulted in attachments to the tendinous sheaths.

In several patients seen by us in Bartonville, the pellagrous erythema was complicated with very marked ecchymoses. These were visible in deeply empurpled patches of otherwise typical areas of erythema. In a negro woman, shown us by Dr. Babcock, in Columbia, an odd-looking, lunar-shaped, ecchymotic area, its concave border upward, was visible beneath each lower eyelid.

The severity of the roughening of the skin of the hands and other regions displayed in the severest types of cases (rugous folds interspersed with furrows of atrophied, scaling, or deeply pigmented and discolored integument) can readily be distinguished in the body after death. This feature is in contrast with some of the severe dermatoses of the body which, post mortem, are scarcely demonstrable.

The pellagrous exanthem is of the order of the toxic erythemas in general, a local expression of a systemic disorder. That its manifestations are awakened by the action of the actinic rays of light upon the exposed surfaces of the skin is incontestable. That this is not solely a reactive result of exposure to such rays is equally clear. Reference is made above to erythema exsudativum, as it is called chiefly in Europe, a disorder due to a systemic infection, yet accompanied by local eruptive phenomena, not invariably, but often, limited to the hands. Arsenical pigmentations and verrucæ of the palms and soles are illustrations of a chemical action not always, but often, having a similar localization. The familiar syphilides of the palms and soles exemplify the localization of symptoms in a disorder which often is exhibited by lesions elsewhere situated, but which for years may be betrayed solely by manual or pedal symptoms. Explanations of these facts are not difficult. The hands and feet are organs not only situated at the greatest distance from the circulatory centres, but also far more exposed than other parts of the body to the accidents of contact with the external world. Dr. Michell called our attention to the frequent congestions of the hands of insane patients, due to their habits.

Many subjects of melancholia and other mental disorders can be seen in the buildings and about the grounds of asylums with their hands depending listlessly by the side and unmoved for hours at a time.

Though the systemic condition is no less essential, the rays of the sun are actually requisite for the production of pellagrous erythema. The result is comparable to that obtained when a chemical reagent is added to a solution containing a suspected ingredient, and which at once demonstrates the presence of the latter by causing a precipitate.

Experiments have been made by exposure of the hands to the sunlight when the organs were partially protected with gloves fenestrated so as to admit the rays to the skin to definite regions only. In these instances the erythema has been limited to the parts exposed to light through the fenestrations. That the sunlight in pellagrous erythema is effective merely because of the weakened resistance of the tissues in the class of patients chiefly liable to the disease is disproved in a photograph shown by Dr. Zeller. The patient, a woman, had paralysis of one hand. The

paralyzed hand was spared; the back of the other hand became the seat of a characteristic rash.

It is especially noteworthy that, given the general toxemia, even feeble exposures to solar light suffice to determine the exanthem. Prolonged exposures are not essential to the awakening of the local efflorescence. This fact was emphasized by the condition of the hands of a patient shown us in the Elgin Asylum. The patient, a woman, suffering from melancholic dementia, had been bedridden for years, and occupied a room in common with another insane woman, also pellagrous. The first patient occupied a bed at the farther extreme corner of an apartment lighted by a single window. The only light accessible for a long period prior to the advent of the pellagrous disorder was furnished by this one window. Yet the hands of this woman, who was suffering from an incoercible diarrhœa, exhibited a perfectly classical picture of the pellagrous "glove," the deep staining of the skin of the hand reaching the wrist, where it was sharply delimited by the cuff of the sleeve worn in the bed. This woman soon after died, and was found, post mortem, to have had fatty degeneration of the liver and other organs.

An interesting control of this fact is furnished in the experience of the Inspector of Insane Hospitals for the State of New York, Dr. Russell, who has examined thirty thousand insane patients under his supervision, presumably as much exposed to sunlight as any of those in Illinois or South Carolina. None of this large number was recognized as pellagrous.[2]

The differential diagnosis of pellagrous erythema is not obscure. Majocchi, in describing the conditions of the hands resembling the pellagrous skin, occurring in patients who are the subjects of chronic alcoholism, declares that the "pellagrous glove," with its distinct limitation at the wrist, is usually wanting; the affection is less often symmetrical; too often extends in an irregular line along the lower forearm; lasts for a longer time; and the ensuing pigmentation is of later occurrence.

The several manifestations of erythema multiforme which affect the hands, both papular and bullous, certainly exhibit different shades of color. The peculiar crimson quality of the isolated papules and tubercles seen in that affection on the backs of the fingers and the hands almost never fuses into a sheet of puffy redness in that situation, never presents the picture, viewed from the back, of the gloved hand. Weeping eczemas of the back of the hand could not be mistaken for a pellagrous exanthem, seeing the invariably irregular contour of the affected patch, its special itchiness, its peculiar color, and persistent ooze on slight provocation.

It may be unsafe at this time to assume that the shade of color seen in a type case of pellagrous erythema, observed at the date

[2] Personal communication.

of full evolution of the eruption, is unique and characteristic. But one is tempted to such a conclusion after close inspection of a hundred patients. In a typical case, to the eye trained in nice discrimination of shades of color, the special hue of the pellagrous skin is unmistakable. There is a quality of reddish-brown in the uniformly stained and puffy integument which confirms the diagnosis. Certainly, the pre-variolous rashes in a menstruating woman, the toxic erythema of Asiatic cholera, and the burns, whether of the first or second degree, produced by the action of solar light, of steam, and of heated water, in the white race, exhibit no such characteristic tint.

In what has been described as the second stage of pellagra, the nervous and psychical disturbances first betrayed in the vertigo, headache, backache, tremor, and lassitude experienced in the early period of the disease, become more pronounced. A profound mental depression, often resulting in settled melancholia, occasionally alternating with periods of psychic excitability, occurs in most instances, and may be followed by stupor and hallucinations. Only a small proportion of patients observed abroad become insane. The symptoms of what has been termed "true pellagrous insanity" differ so widely that at this point the student of the disease is confronted with a confused multiplicity of symptoms, contrasting with the uniformity of the cutaneous lesions to which attention has been directed. While the body-weight in these cases decreases, the patient often refusing food, he frequently becomes the victim of hallucinations, delusions respecting guilt, persecution, and attempts upon his life. In rare cases epileptiform and even cataleptic seizures occur. Seeing that pellagra occurs among the tuberculous, the syphilitic, the subjects of tabes and tabo-paralysis, of dementia paralytica, of uncinariasis, of amœbic dysentery, of bilharzia disease, and of other affections, it is not surprising that a distinct and characteristic imprint of the pellagrous poison upon the brain and nervous system does not seem to have been clearly determined.

Scheube and other writers have called attention to the tendency of demented pellagrous patients to commit suicide by drowning (hydromania), for the reason, it is surmised, that the subjects of the hallucinations common in this disorder are impelled to the act by a vague desire to cool the burning mouth or the irritated skin. But a comparison of statistics leads to the conviction that there should be some reserve in accepting these conclusions. From the admirable *Dunning Report of Pellagra in Italy*, it appears that in that country but 10 per cent. of pellagrous patients become insane. Now, the deaths from pellagra per 100,000 inhabitants in Lombardy, which may be called the home of pellagra, amounted in 1907 to a total of 10.4. In Veveto, which suffered more than the other provinces, the percentage of deaths from pellagra in 100,000 of

inhabitants for the same year was 18.4, the highest obtaining in any of the provinces for the year named. Granting that but one in ten of these patients died insane, and supposing that of these even one in three managed to commit suicide by drowning, the deaths from that cause would only equal the number (0.6) of suicides by drowning in each 100,000 of sane and insane inhabitants of the entire United States for the same year, the number for each year from 1900 to 1907 being practically the same.

Even allowing for the possibility that some victims of pellagra not insane ended life by drowning, and, further, assuming that other patients under proper surveillance made futile attempts at self-destruction, the figures yet speak for themselves.

The gastro-intestinal symptoms of pellagra, as has been seen, occur in all stages of the disorder, and not rarely constitute its most intractable feature. Often the characteristic diarrhœa, equally severe day and night, accompanied by meteorism and pyrosis, develops simultaneously with the erythema. The redness of the tongue, whether of the mild or of the "bald" variety, which results from an exfoliation of the buccal epithelium, in some cases is associated with profuse salivation. In one of the patients, a colored woman, shown us at Columbia, the saliva flowed freely from the lips. Dr. Babcock, in this connection, pointed out in some of the patients a peculiar, pinpoint-sized, blackish or bluish-black pigmentation occurring at the apex of some of the filiform papillæ of the tongue, an observation confirmed by Watson in a number of negro patients (Lavinder's "stipple tongue"). In some cases these conditions of the buccal membrane have coincided with similar changes in the rectal and vaginal mucosa. In many instances patients exhibit the severest symptoms of dysentery, with bloody evacuations. In the terminal stages of pellagra, peristalsis of the intestine may cease. In exceptional cases there is constipation rather than diarrhœa. Nesbit, reporting the results of his stomach analyses in 10 cases, found 4 showing marked diminution of acidity of the gastric juice, and 5 with excess of mucus. There did not seem to be any change in motility.

The so-called third, or terminal, stage of pellagra has been described as typhus pellagrosus. The condition is one in which there is merely grave accentuation of the symptoms declared in the other artificially classified stages of the disease. No typhus, as that term is now understood, is present, and Bacillus typhosus (Eberth) is not demonstrable. The patient may have a symptomatic fever, declared for the first time during the progress of the disease. He is usually profoundly prostrated; there is extreme weakness from the intestinal flux which has preceded, with emaciation and stupor, or mild delirium. The diarrhœa at the last may intermit.

A striking feature of this terminal stage is opisthotonos, the patient lying upon the bed with the head forcibly extended, the

general musculature in a state of great rigidity. Oddly enough, this is one of the few constant symptoms of the disease in its final stage. Coincidently, there is extreme tenderness of the loins and back, less directly over the spinal region than over the points where the spinal nerves make exit from the vertebral canal, a few inches from the spines on either side. This was exceedingly conspicuous in one of Dr. Watson's patients shown us, to whom reference has been made, a negro lad in the last stages of pellagra who, attempting to stand and walk, accomplished these acts with a rigidity of the muscles of the trunk and extremities simulating the symptoms seen in dengue fever.

When investigating the neurological phenomena of pellagra, Dr. Bassoe, of our commission, was able to make a careful examination, extending through the greater part of two days, of a group of selected patients in the Peoria State Hospital.

Practically all of these patients were in an advanced state of dementia, utterly precluding inquiry into their subjective symptoms, especially those relating to sensation. Inasmuch as all the subjects were reported to have been insane for years before the appearance of symptoms suggestive of pellagra, they could not be suffering from true pellagrous insanity, and their mental state was not of special significance in connection with this inquiry. In almost all the cases, examination, not merely of sensation, but of all functions requiring coöperation on the part of the patient, being out of the question, we were limited to testing the reflexes, and even this in many instances was difficult. The chief aim was to reach some conclusion respecting the frequency of signs of degeneration in the cord or peripheral nerves.

Fourteen men and eleven women were examined. Four men and eight women presented sufficiently marked increase of the tendon-reflexes to suggest the probability of some degree of degeneration of the pyramidal tracts. One of these men and four of the women had a more or less constant Babinski sign. One woman and one man presented signs of degeneration of the posterior columns alone, as most of the tendon-reflexes were lost; others were greatly reduced; the woman also was extremely ataxic. One woman probably had a combined degeneration of the pyramidal and posterior tracts, as there was loss of tendon-reflexes, with an inconstant Babinski sign on one side. No instance of local or multiple neuritis was observed. We could find no reason to believe that any of the cases with changes in the reflexes were instances of combined pellagra and tabes, spinal syphilis, multiple sclerosis, or other independent organic nervous disease. The following are examples of the three groups encountered:

A. *Probable Pyramidal Tract Degeneration.* Case I.—Demented male epileptic, aged thirty-seven years, admitted April, 1902; previously at a poor farm and another State hospital. Insane for nineteen years. Diarrhœa and erythema of the hands during the

past summer. The hospital record mentions increased tendon-reflexes and positive Babinski sign on August 31, 1909. Examination on October 10 revealed increase of all tendon-reflexes without clonus; inconstant Babinski and Oppenheim signs; pupils react to light. There is slight swaying in Romberg's position, but the patient walks well and the heel-knee test is as good as can be expected in a demented subject. A note was made on October 31 that he had had stomatitis and diarrhœa for several weeks, and lost forty pounds in weight.

B. *Posterior Column Degeneration.* Case II.—An elderly demented woman developed characteristic skin lesions in August, 1909. Ataxia is so marked that she cannot walk or stand alone. The wrist, elbow, knee, and ankle-reflexes are lost. No Babinski sign. No involuntaries. Pupils normal. Characteristic erythema of the hands and face when examined on October 10.

C. *Combined Degeneration.* Case III.—A woman, aged fifty years, was admitted in November, 1908, with a history of having been insane for fourteen months. On admission she was fairly well nourished and the tendon-reflexes were normal. The psychosis was melancholia of involution. On August 27, the wrist- and elbow-reflexes were recorded as normal; the knee-reflexes as increased. No Babinski sign at that time. On October 10 she was emaciated, with severe stomatitis and diarrhœa. The wrist-jerks and the left elbow-jerks were absent; the right elbow-jerk, weak. Knee- and ankle-jerks absent. Inconstant Babinski sign on the right side; normal flexor response on the left side. The pupils reacted rather sluggishly to light. She died on the following day. No necropsy. It seems probable that the pyramidal tracts were first involved, causing increased knee-reflexes. Later, the posterior columns degenerated sufficiently to abolish nearly all of the tendon-reflexes.

Nine patients affected with typical pellagra were selected at this time by Dr. Davis, of our commission, for blood examination from the abundant material available. They were fairly representative cases, and should present in a general way the blood picture as it appears in the disease as it existed in Peoria.

BLOOD EXAMINATION IN CASES OF PELLAGRA.

Blood cultures.	Erythro-cytes.	Hemo-globin.	Color index.	Leuko-cytes.	Polynu-clears.	Small mono-nuclears.	Large mono-nuclears	Eosino-philes.	Baso-philes.
Negative	4,514,000	86	0.95	7,600	79.6	12.3	6.4	1.2	0.5
"	2,816,000	71	1.20	24,000	74.6	13.7	11.7	0	0
"	4,736,000	86	0.90	20,600	67.3	19.1	19.6	0	0
"	4,616,000	77	0.84	15,500	59.6	25.4	14.5	0.5	0
"	4,040,000	86	1.05	14,600	70.0	23.1	6.4	0.5	0
"	3,760,000	78	1.04	13,500	77.5	11.4	10.6	0	0.5
"	3,390,000	76	1.12	13,050	65.5	28.0	6.6	0	0
"	4,040,000	77	0.95	13,100	65.8	9.2	24.2	0.8	0
"	3,464,000	77	1.10	14,300	74.1	20.0	5.5	0	0.4
Average	3,930,700	79.3	1.01	15,140	69.77	18.02	11.72	0.33	0.16

Blood cultures were made, using for media ascites broth and plates of agar. The blood, obtained by withdrawing 5 to 10 c.c. from a vein at the elbow, was distributed into large tubes of broth, to which ascitic fluid had been added in the proportion 4 to 1, and into melted agar tubes, which were at once poured into plates. The tubes and plates were then placed under aërobic and anaërobic conditions and examined from time to time for growth. In all cases the results were negative. Generally, the cases showed a slight grade of anemia. The red cells varied from 2,816,000 (Case II) to 4,736,000 (Case III). The hemoglobin (the Dare instrument was used in all cases) varied from 71 per cent. to 86 per cent. The color-index ranged from 0.84 to 1.2, five of the cases having an index a trifle over 1. In Case II the index was sufficiently high to suggest the type of pernicious anemia. In this case the red cells were counted twice and two hemoglobin determinations made, with substantially the same results. The average index of the nine cases is 1.01.

In connection with these results, the fact should be noted that nearly all of these were bedridden patients, in whom the peripheral circulation was sluggish. This would tend to give higher readings, and due allowance should be made for this condition.

The number of white corpuscles in this series of cases is strikingly uniform. The lowest count was 7600 (Case I), and the highest was 24,000 (Case II). In most of the cases the number ranged from 13,000 to 15,000. Differentiation did not give marked variations from the normal. The polynuclear cells varied from 59.6 per cent. to 79.6 per cent., the average in the 9 cases being 69.7 per cent. The small mononuclears ranged from 9.2 per cent. to 28 per cent., averaging 18.02 per cent., and the large mononuclears varied from 5.5 per cent. to 24.2 per cent., averaging 11.72 per cent. This is somewhat in excess of the normal number of large mononuclears, which is usually given as 5 to 6 per cent. The increase, as shown by the table, occurred in 5 of the cases, the other 4 giving normal percentages of these cells. It is especially noticeable in Case VIII. Basophiles were rare, as were also the eosinophiles. In only 4 of the cases were the latter found, and then usually only after counting several hundred leukocytes. Over a thousand leukocytes were counted in some of the cases without finding a single eosinophile. Especial attention was given to these cells, for the reason that an eosinophilia is often found in various skin diseases, and also in conditions in which the intestinal tract is infested by animal parasites. Inasmuch as intestinal symptoms were common in these cases,[3] in addition to the skin lesions, this point seems noteworthy. Myelocytes were not found in any of the

[3] Postmortem examination in Cases III, VI, and VII of this series revealed inflammatory or ulcerative lesions in the intestinal tract. In these cases also amœbæ were reported to be common in the stools.

cases, nor were nucleated red cells encountered. The erythrocytes in stained preparations gave no evidence of polychromatophilia or poikilocytosis, and basophilic degeneration was not observed.

Compared with the observations made by others on pellagra cases, the results here recorded agree in that a mild grade of anemia was found, and also in the fact that many of the cases gave an increase in the large mononuclear cells. According to Lavinder and others, a leukocytosis is not usually found, except in association with secondary complications, which not infrequently occur, especially in the later stages of the disease. Postmortem examination of some of these patients disclosed, for example, lesions of the intestine which may have been responsible for the leukocytosis observed. Such lesions, however, are not rare. If they constitute an essential part of the pathology, the fact has not been definitely established.

These results are practically those reported by other observers at the Pellagra Conference. For the most part (there was but one exception) the eosinophiles were unmistakably few and the mononuclears numerous, the increase being in cases noteworthy. Microörganisms, save in the exceptional hematozoa cases, were absent. Howard Fox, after an examination of 30 cases in Columbia by the Noguchi modification of the Wassermann test, found that in pellagra there was no positive reaction. When weak reactions were obtained, they were without difficulty distinguishable from those secured in syphilis and lepra.

The ocular symptoms in pellagra have been studied in America by Seiler, Watson, and Welton, of Peoria, who kindly showed us the record of his findings, the pellagrous conditions of the eye being compared with carefully made control observations. Pupillary changes with bilateral or monolateral mydriasis, conjunctivitis, retinitis, inflammation of the optic nerve, and especially chorioiditis, are not rare, the grade of the eye changes in general, as might be expected, presenting severity corresponding with the general symptoms. In one of the patients examined by us photophobia was pronounced. In a small percentage of the fifty-five patients examined by Welton, there was paralysis of the ocular muscles. In none were eye-symptoms recognized as pathognomonic of pellagra.

Though pellagra is not an inherited disease, its occurrence in children is noted by many writers on the subject. Pellagrous women often abort; others bring into the world infants who, when living in pellagrous districts, speedily develop the malady, the offspring being not rarely stunted, as well as deformed.

The fruit of pathological research in pellagra serves to illustrate in a conspicuous manner the marked absence of any constancy in the changes wrought by the disease. The earlier cutaneous alterations are similar to those found in the exudative erythemas, while in the terminal stages the microscopic picture is practically

that presented in the senile skin. Depending on the type of the inflammatory reaction and the stage of the process when the examination is made, the histological changes vary from those found in simple erythema to those seen in marked bullous dermatitis. Still later, atrophy of the papillæ and sclerosis of the vessels of the corium with hyperpigmentation and hyperkeratinization of the epidermis are found, the latter identical with those found in the senile skin. The parenchymatous neuritis of cutaneous nerves recorded by Déjerine has not been confirmed by other observers.

Scheube, Sandwith, and Tuczek agree that in many cases there is pigmentation of many of the viscera, wasting of the muscular and fatty tissues (especially atrophy of the muscular coats of the intestine), brown atrophy of the heart, atheroma of the larger vessels, hepatic enlargement, splenic shrinkage, fragility of the ribs (Lombroso), cirrhotic changes in the kidneys, and, as respects the nervous system, either no perceptible changes, or in the brain, cord, and meninges evidences of chronic inflammation, subarachnoid hemorrhages, cerebral atrophy, and symmetrical sclerosis of the posterior columns, especially those of Goll. Occasionally the postero-lateral columns in the dorsal region are similarly involved. Marie believes that these cells are, in general, primarily involved.

Harris ascribes the variability in the recognized organic lesions to the extreme chronicity of the disease and to the further fact that most postmortem observations have been made in subjects who were for a long time victims of the malady. His observations include, besides those enumerated above, atrophy of the pancreas, softening of the cord, signs of Belmondo's "meningo-myelitis acuta," with marked degenerative changes in the myelin-sheaths of the nerves, of the nerve cells of the gray substance, and of the ganglia. Peripheral nerve changes have not been recorded.

The following is, in brief abstract, the record of an autopsy made by us in October, 1909, on one of the Bartonville subjects. It illustrates the inconstancy of postmortem results in some of these cases. The negative findings are not enumerated:

W. E., aged forty-two years, developed pellagra early in August, 1909. The cutaneous and other symptoms subsided, but recurred four days prior to the date of the autopsy. Recent symptoms included severe abdominal pains, diarrhœa, and a scaling dermatitis of the hands.

Anatomical Diagnosis. Moderate grade of dermatitis of the dorsum of the hands; right serofibrinous pleuritis; healed tuberculosis of the pleura; chronic suppurative cholecystitis; chronic ascending cholangitis; cholelithiasis; multiple abscesses of the liver, with rupture into the peritoneal cavity; acute suppurative peritonitis; acute splenitis; acute nephritis; icterus; pigmented Peyer's patches; acute purulent tracheitis and bronchitis; fibrous adhesions about the gall-bladder and in the lesser peritoneal cavity; obstruc-

tion of the common bile duct. *Bacteriology*: From the bile, peritoneal fluid, heart's blood, pericardial and pleural fluids, Bacillus coli communis was obtained in pure culture.

Nichols found a very high percentage of protozoal infections of the colon in the pellagra patients examined by him in the Peoria State Hospital, and at the Pellagra Conference exhibited sections of intestine with unmistakable ulceration of the mucosa, the result of amœbic dysentery. Schreiber, however, in three patients who were not amœbic, recognized, post mortem, superficial ulcerations of the mucosa of the colon.

A survey of the records of pellagra in this country suggests an inquiry which seems to have attracted but little attention up to the present time, as to whether the majority of patients in America were first insane and later became pellagrins, or whether they were first pellagrous and later, either as a complication or a consequence of the affliction, became insane. This question is somewhat intricately bound up with another, namely, for how long a time has pellagra actually existed in the United States?

Some of the physicians of the South are disposed to believe that pellagra has claimed its victims in this country for twenty-five years. Williams and Mobley cite cases which seem to have been well-marked instances of pellagra, occurring twelve and ten years ago. Watson exhibited to us in Columbia a negro boy, twelve years of age, whose symptoms were of the most pronounced and classical type—cutaneous, digestive, nervous, and ocular. He had suffered for five years, and for two years continuously with cutaneous lesions (pellagrous "gloves," "boots," Casal's "neckband," etc.). Several superintendents of asylums are reperusing letters and reports sent in the past by members of families to whom either the bodies of dead or restored patients had been returned, complaining of maltreatment of these individuals by attendants through scalding the hands and other parts of the body—instances of what is now believed to have been pellagra. Zeller cites one such case in which a nurse had been dismissed in disgrace, but was restored to duty after the facts were more fully understood.

On the other hand, the evidence that many inmates of asylums were insane before they became pellagrous seems conclusive. These are often ex-inmates of workhouses, pauper asylums of different sorts, debilitated long before their admission to the institution where they were recognized as pellagrous, their lives rounding out a full measure of misery and physical degeneration. The mouths of many are in the worst possible condition. One cannot conceive of a class of subjects more fit for the invasion of the special poison of pellagra. The fact that the insane may become pellagrous is by no means newly attested. Brière de Boismont, Billot, and others describe in detail pellagra as "manifested during the course

of mental disease." Baillarger cites cases in which pellagra appeared some time after the admission of insane patients to the asylums in Turin.

An important point in favor of the conclusion that the insane of some of our asylums have recently become pellagrous is to be found in the character of the skin symptoms. It is within bounds to declare that the most of the cases seen by us showed face, hand, and neck symptoms belonging to the early rather than the late pellagrous stages, as evidenced by the vividness of the erythema and the absence of the atrophic sequels of the invasion of the skin.

It is noteworthy in this connection that the same question respecting the prior existence of pellagra was asked when the malady first appeared and spread in Italy to such an extent as to arouse the attention of the physicians of that country. It has, however, been generally accepted that there could have been few cases observed by medical men before the middle of the eighteenth century, as the symptoms of the disease were then scarcely enumerated in literature.

The cause of pellagra is unknown. It would exceed the compass of this article to set forth the arguments pro and con of the "zeïsts" and "antizeïsts," namely, of those who do and of those who do not believe that the ingestion of maize is responsible for the disease. On the one hand stands Sir Patrick Manson, who categorically disputes the position that either the nutritive ingredients of sound corn, or toxin which it may contain, or even fungi or bacteria (Bacillus maïdis, Ustilago maydis, Bacillus pellagræ, Penicillium glaucum, Aspergillus flavescens, fumigatus, varians, etc.) accidentally developed on the grain are, any of them, effective. It is true that one of his arguments is weakened today by his citation of the United States as a corn-eating and pellagra-free community. It is certain that those who have never consumed corn have had pellagra. It is equally certain that experimental consumption of spoiled corn by man has not resulted in the development of the disease. Further, it is undemonstrated that cattle suffering from "blind staggers" and other disorders, as well as chickens dwarfed after a diet of "pellagrozein," as Lombroso termed it, were victims of pellagra.

On the other hand, to the mass of evidence in favor of some connection between the consumption of maize and pellagra collected by skilled observers and scientific men in various parts of the world, a conservative judgment cannot fail to assign value. The National Pellagra Conference held in Columbia (1909) assumed a judicious position by declaring: "That while corn is in no way connected with pellagra, evidences of the relation between the use of spoiled corn and the prevalence of pellagra seem so apparent that we advise continued and systematic study of the subject, and, in the meantime, we commend to corn-growers the great importance of fully maturing corn on the stalk before cutting the same."

Recognizing, however, a fact of importance in this connection, namely, that pellagra has occurred in persons living on a diet consisting largely of durra (Indian millet, Guinea corn), it is probable that a much wider scope must be allowed for the play of the special toxin effective in the production of the disease, if its etiological factor is ever demonstrated to be closely related to a cereal diet.

The full report by Dunning on Pellagra in Italy would seem to furnish overwhelming support to the proposition that maize is responsible for pellagra, were it not for the evidence it presents of efforts on an enormous scale put forth by the Italian Government, not merely in the direction of excluding maize, and especially spoiled maize, from the dietary of their peasantry, but also in the line of a wide improvement in the general hygienic environment and food of the people. The admittedly impoverished condition of the great mass of sufferers points unmistakably to the predisposing causes of the malady. The setting of these aside in large measure has naturally produced a noteworthy change in the statistics of the disease in Italy. How far these can be cited as arguments in favor of the zeïstic origin of pellagra is questionable. The indisputable facts in this connection are the occurrence of the disease as an endemic; its practical limitation within definite geographical limits; its involvement of men, women, and children, at all ages, but especially of adults between the third and fifth decades of life; and that its victims everywhere belong to the class of those whose resistance is weakened by poverty and such of its attendant ills as insufficient and improper food, exposure, and unremitting toil.

The brilliant successes in the management of pellagra have been secured by prophylaxis. Amelioration of the environment, food, and mental state of pellagrous patients living in pellagrous districts has worked surprising results.

The Italian campaign against pellagra has been conducted by enactment of laws providing for inspection and condemnation of suspected food imports; by requiring registration of all pellagrous cases; by the establishment of pellagrological commissions, such as that recently authorized by the Illinois Legislature;[4] by founding pellagrosarios, institutions for the care of the sick; by distributing proper food to destitute families; by erecting "economic kitchens" and rural bakeries, where food of proper quality is supplied at a low price; by appointing commissions (*Cattedre ambulanti*) for instruction and encouragement in improved methods of agriculture; and by providing public desiccating plants for drying maize, and public storehouses for its preservation. An elaborate system of

[4] The Governor of Illinois has appointed a commission to report upon pellagra in the Charitable Institutions of the State, consisting of the following-named gentlemen: Dr. Frank Billings, Chicago; Dr. J. L. Greene, Springfield; Dr. Geo. W. Webster, Chicago; Dr. H. S. Grindley, Urbana; Dr. Howard T. Ricketts, Chicago; Dr. Oliver S. Ormsby, Chicago; Dr. H. Douglas Singer, Hospital; and Dr. W. J. McNeal, Urbana.

public education has also been put in operation by lectures and distribution of pamphlets. The happy results are worthy of study as well by the economist as by the physician.

Compared with these, the fruits of medication of those who are infected are scarcely worth naming. Arsenic by the mouth and by hypodermatic injection, atoxyl administered by both methods, quinine, strychnine, iron, have been both praised and adjudged of little value. Drs. Cole and Winthrop, employing transfusion with the blood of both cured pellagrous and non-pellagrous subjects, seem to have secured satisfactory results in a few cases. Today the best accepted treatment of the disease is that which is indicated in individual cases by the symptoms presented, always having in view the imperative demand for improved nutrition.

The extent of the prevalence of pellagra in the United States is set forth in the observations of Lavinder, who has had opportunities for the observation of the disease in all parts of this country. The first cases were reported by Dr. Gray, of New York, and Dr. Tyler, of Massachusetts, at the meeting of Asylum Physicians, held in Washington, D. C., in 1863 and 1864. Before these dates there had been reports of isolated cases occurring near Halifax, N. S. I was present at the meeting of the American Dermatological Association, in 1902, when Dr. Samuel Sherwell, of Brooklyn, reported two cases occurring in Italian sailors found pellagrous after entering the port of New York. Lavinder's list of those of the States where pellagra is believed to have occurred includes the names of thirteen, mostly Southern, to which Illinois and other States have since been added, making a total believed to be sixteen. Most of the cases reported are in public institutions of one kind or another, chiefly asylums for the insane. At the date of the appearance of Lavinder's leaflet it was believed that a total of one thousand cases had been recorded. The number has since increased. Dr. Kerr estimates that there were five thousand pellagrins in the United States in the year 1909.

Respecting the prognosis of pellagra, the percentage of mortality among American patients seems to be nearly 35 per cent. of those affected. Unfortunately, the larger number of fatal cases has occurred among the insane presumably affected with the disorder after admission to the institutions reporting the fatality. Statistics of pellagra in its terminal stages in this country, where the course of the disease from onset to conclusion was wholly and purely due to the pellagrous poison, are not available. Randolph, basing his conclusions upon the Florida cases, believes that about one in every four or five patients recovers. Of the series of cases studied by Siler, 22 per cent. died, 10 per cent. were failing, and 17 per cent. improving at the date of his report. In a personal communication received from Dr. Zeller since the adjournment of the Conference, he reports the death of several patients observed by us when per-

mitted to make the observations recorded in this article. Most authors agree as to the curability of the disease in its earliest manifestations, chiefly by the aid of the generous regimen suggested above. Fritz, director of the Pellagrosario at Inzago, in a long experience, has seen but two complete cures of fully developed cases.

Physicians in all parts of the United States are now somewhat anxiously regarding the possibilities of the future respecting the progress of pellagra in this country. The history of the disease in the past points with emphasis to the fact that in countries where it has once attacked the population it recurs with somewhat alarming regularity, save when such elaborate measures of repression have been adopted as those briefly outlined above in connection with the campaign against pellagra in Italy. What will be the issue of the oncoming spring and summer when, according to the common mode of the malady, its recrudescence in a severe form might be anticipated? It is probable that there may be during the year 1910 a considerable increase in the number of cases reported.

But he has poorly comprehended the economic equations of our national resources who looks to see pellagra work such havoc in this country as among the smitten peasantry in the provinces of Bergamo, Brescia, and Venetia. It has been aptly said of the poor of America that they do not know what poverty is. Incredible as it may sound to those unfamiliar with the fact, a large number of the applicants to public charities, in the Northern States at least, are food-poisoned by sheer glut. They are not even strangers to the gout.

The lessons of pellagra are writ too large to be neglected in any wide measure by an intelligent people. Its cause, as yet undetermined, will be revealed; its prophylaxis is already understood; it certainly will be relegated to that path whither uncinariasis has been consigned, and along which yellow fever and tuberculosis are already disappearing.

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HIGH CALORIC DIET IN TYPHOID FEVER.

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The present death rate of typhoid fever is very low, notwithstanding many serious complications which are possible. But there is much to be gained in comfort to the patient. The classical three weeks cannot be aborted, but the prospect of an average lower temperature and pulse rate with lessened meteorism, toxemia, and delirium is very alluring. By due regard for the dietary, this end can be achieved in all but a few severe cases.

My object is to consider this subject from the standpoint of the physiologist and at the same time take account of the altered conditions in the intestinal tract and the deviations from normal metabolism. If the subject is approached with a spirit of fairness and with a desire to examine closely the more exact experimental evidence, one can hardly escape the conclusion that the use of milk and various "peptone" preparations is based on prejudice and precedent, and has little else to commend it. To recommend indefinite quantities of foodstuffs without inquiry into their chemical architecture and the needs of the patient is inexact and unscientific. Shaffer[1] has estimated that the typhoid fever patient rarely receives more than 50 per cent. of food necessary to supply dynamic needs. This usually contains at least three times more nitrogen in proportion than would be advisable to allow a healthy individual. Naturally the balance of the dynamic needs must be met by the body tissue with consequent loss of weight and increasing weakness.

The use of milk—plain, fermented, or digested—is strongly intrenched in American practice, and it is difficult to obtain consideration of other foodstuffs. The argument that milk is "easily digested" loses force in direct proportion to the number of curds in the stools and the degree of meteorism. If sufficient is given to meet dynamic needs, the bulk is almost prohibitive. It neither protects against nitrogen loss (if that is desirable) nor does the chemical structure of the casein molecule permit of its rational use.

The favorable results obtained with Seibert's[2] soup diet led to this article. He does not use milk. The relative amounts of protein, fat, and carbohydrate are difficult to estimate, but there is a commendable increase in energy producing elements. The cases reported are sufficiently numerous to draw satisfactory conclusions concerning the death rate. But most convincing to the judicial observer is the frequent absence of necessity for baths and

[1] Jour. Amer. Med. Assoc., 1908, li, 974.
[2] Medical Record, June 20, 1908.

stimulation, and the absence of those symptoms which make the life of the typhoid fever patient miserable.

THE DIGESTIVE SECRETIONS IN FEVER. In general, typhoid fever is a disease characterized by ulceration of Peyer's patches—the organs of protein assimilation—diffuse catarrh of the intestinal mucosa, and by a Bacillus typhosus bacteremia. Experimental medicine has shown that the glandular secretions of the digestive tract are diminished or altered. Jawein says that the total quantity of salivary juice is less than normal; it is often acid, and ptyalin is absent. Dry mouth and sordes are always present.

Kraus[3] has this to say of the gastric secretions: "The amount of HCl is so small that the affinity of the food is not satisfied. Organic acids contained in the food or derived from it by fermentation preponderate in the chyme. Von Noorden obtained, *together with numerous negative results*, distinct evidences of HCl during the high fever of erysipelas and scarlet fever, provided large amounts of salt and pepper were added to the meat taken." According to Sticker and Zweifel, the power of absorption is diminished, but the motor functions seem to be undisturbed.

The hepatic functions in typhoid fever are also altered. Post-mortem degenerative changes are found and acute yellow atrophy may follow intense toxemia. There is a diminution in the quantity of the bile (Bidder and Schmidt), it is more viscid, and contains an abnormal amount of mucus (Pisenti). Naturally there exists no evidence as to the integrity of the pancreatic secretion or the succus entericus. That these digestive juices, in common with others, are diminished in quantity and altered in quality, particularly in typhoid fever, is the natural and justifiable assumption. There is an admitted 10 to 12 per cent. decrease in the digestive capacity of the typhoid fever patient for all classes of foodstuffs (von Hoesslin). With the above facts drawn from precise observation before us, are we justified in believing that 10 to 12 per cent. covers the amount lost?

It is my purpose to omit discussion as to the power of the fever patient to digest and assimilate fat and carbohydrate. There is not the necessity for the use of fat, notwithstanding its high caloric value. Its tendency to produce digestive symptoms is a positive contra-indication. As to starches and sugars the question will hardly arise. Von Leyden and Klemperer, von Hoesslin, Folin, and others believe that it is normal within the above percentage, and the evidence on which their conclusions is based is seemingly conclusive. On the other hand, protein assimilation in fever will demand some detailed attention, for it is important to know whether

[3] Where references are not given in detail, they may be found either in von Noorden's "Metabolism and Practical Medicine," Lusk's "Science of Nutrition," or in the papers definitely indicated. Such sources of information have been freely summarized with a view to presenting the subject as cogently as possible.

the benefits from its use overshadow the disadvantages. The present view that digestion and assimilation of protein is normal within 10 per cent. rests on the accuracy of the nitrogen balance as an experimental procedure. Does nitrogen which has disappeared en route through the fevered digestive tract mean normal utilization?

PROTEIN ASSIMILATION IN FEVER. Accepting Chittenden's standards for the purpose, a normal man ingesting daily 60 grams of protein (about 11.5 grams of nitrogen) and sufficient fat and carbohydrate to yield 2000 to 3000 calories, will pass 2 grams (or less) of nitrogen in the feces. The difference—all but one gram, more or less—will be eliminated in the urine. This is assuming that his work is light, and that other factors, such as external and internal temperature, etc., are medium, normal, and constant.[4] It is not possible to differentiate the sources of fecal nitrogen in a given case. According to Voit, who tied off intestinal loops in dogs, most fecal material is true excrement from the walls of the intestines or glands emptying therein. Strassburger[5] estimated that one gram of nitrogen in the normal stool is contained in the bodies of bacteria, which may have arisen from food or secretion nitrogen. There is also nitrogen to be found in desquamated cells, carbon nuclei fractions resulting from bacterial activity and other minor sources. Further, in typhoid fever there may be blood and reparative serum exudates which have survived the destructive influences above mentioned. So economical is the organism in the use of foodstuffs that there is very little nitrogen residuum from intake. It is probable that fecal nitrogen may vary in its distribution at different times and in different individuals, and that the distribution may be materially altered within a short period.

An increase in protein intake does not cause an increase in the nitrogen of the feces until the capacity for assimilation is far exceeded. The first effect is increased nitrogen exchange, and the evidences appear in the urine. As soon as it reaches the lower limit of heat requirements in the starving man, oxidation and heat elimination increase, and the thermo-regulating mechanism is called into play. This is the effect of the specific dynamic action of protein as demonstrated by Rubner. The second effect of the overuse of meat is usually increased intestinal putrefaction, with increase of its products in the urine and sometimes in the feces. It is only during recovery from disease, growth, and prolonged muscular exercise that the body is able to retain any quantity of nitrogen by increased protein feeding.

Approximately 82 per cent. of the urinary nitrogen is eliminated in the form of urea. This substance has no single source. A

[4] Rieder found that a man on a non-nitrogen diet passed 0.54 to 0.87 gram of nitrogen in the feces daily. These values are about 0.5 gram greater than Müller found in the starving Cetti. This is the minimal value of secretion nitrogen not reabsorbed.

[5] "Die Faeces des Menschen."

portion is derived from the liver and in part represents unused residual ammonia fractions arising as required alterations in molecular form take place in the change from the food to body proteins. A portion is derived directly from food proteins by simple hydrolytic splitting, such as may occur after the ingestion of arginin. A portion is the end-product of cellular metabolism. Urinary creatinin is exogenous and endogenous, the latter, according to Folin, being a measure of cellular metabolism. The same is true of xanthin bases. Sulphuric and glycuronic esters are products of intestinal putrefaction.[6]

The urinary nitrogen of the fever patient shows alteration in distribution. The total amount is increased proportionately to the intake. The quantity of endogenous purins increases with the fever (Mandel), and proportional to the whole nitrogen output. Ammonia in combination with organic acids always increases, and often at the expense of urea ammonia. This ammonia excretion shows a total weight from 2 to 6 grams as against 0.7 gram in health. The creatinin nitrogen on a creatinin-free diet shows a ratio to total nitrogen of 0.2 to 4.5 as against 5 to 7 in health (von Noorden). The excretion of indican may be increased by eight or ten times over the health maximum. In severe infections the distribution of nitrogen may be so altered as to resemble the toxemia of pregnancy (Ewing).

KIDNEY CAPACITY IN FEVER. The reasons thus far advanced to show the limitations of the nitrogen balance more particularly involve problems of metabolism. There are some others which involve the activity of special organs. The quantitative elimination of nitrogen by the kidneys varies in a most unaccountable manner, following to some extent the cyclic elimination of health, but without the precise periodicity. The variations, however, furnish considerable leeway for error, unless the period of observation is prolonged. Epicritical elimination of nitrogen, following the termination of an infective process seems to point in the same direction.[7] The possibility that nitrogen may be retained in the form of excrementitious products, secondary to the irritation of infection must be admitted, and may under these circumstances be the equivalent of latent uremia.

NITROGEN EXCRETION BY THE SKIN DURING FEVER. Nitrogen is excreted in the perspiration, the whole amounting from 0.2 to 0.66 gram daily (Atwater and Benedict). Increase in nitrogen elimination usually follows increase in the quantity of sweat, as the

[6] The nitrogen in these compounds is small. The significance lies in the fact that they represent a definite amount of protein, disintegrated by extradigestive processes, which also may be represented in the ammonia output.

[7] Epicritical elimination of nitrogen has been explained on different grounds. As an example of retained nitrogen from non-elimination, Schondorff found that after feeding a dog an abundance of meat, there was 40 grams nitrogen accumulation in the tissues "in the form of water free extractives and 20 grams of urea nitrogen."

result of muscular exercise. The external temperature and humidity also have their effect. Argutinski found that he excreted 750 mg. perspiration nitrogen in the summer and less than a third of that amount in autumn. These results can hardly be applied to an infective process, because circulatory disturbances are an inevitable accompaniment. The contraction of peripheral arterioles not only inhibits conduction and radiation, leading to retention and fever, but the supply of sweat-producing materials to the skin is diminished. There is, therefore, a diminution in refrigeration. By measurement, the evaporation of water from the skin during fever is normal, but observations on this point do not seem to be conclusive. Admitted as true, the effort of the organism to lose heat through evaporation neutralizes the contraction of arterioles from infection. Proportionate to the rise in temperature, the amount of perspiration is therefore diminished. From a clinical standpoint, this view is hardly satisfactory. One can scarcely watch the periodic and irregular drenching of bedclothes without wondering whether nature has overcome the tendency of the infection to curtail evaporation, and thus the laws for the irregular excretion of urinary nitrogen become operative for the skin. If uncalculated in the nitrogen exchange, the uppermost limit of sweat excretion during muscular activity would lead to an error of 12 or 15 per cent. on Chittenden's diet.

Bacterial Disintegration of Protein. F. Müller suggested that the amount of body protein destroyed by bacteria was sufficient to take into account, but there has never been general acceptance of this view. Of more importance are bacterial processes in the intestine during fever, and especially typhoid. The withdrawal of digestive juices and delay in digestion of protein is an opportunity which intestinal bacteria do not neglect. This is shown by the large excretion of urinary aromatic sulphates, the meteorism, and foul stools. We are unacquainted with bacterial processes in the intestine during typhoid fever. We know nothing of possible powers which Bacillus typhosus, acting alone or in symbiotic activity with Bacillus coli or anaërobics, may have in disintegrating foodstuffs and thereby producing a toxemia independent of but augmenting the intoxication of the disease. The amount of protein lost to the organism in this manner cannot be estimated, but it must be considerable on a high protein diet.

Conclusion. It is not forcing the conclusion to say that a daily nitrogen balance does not necessarily indicate proper digestion, absorption, and utilization of protein in the fever patient. "It is by no means certain that the amount of nitrogen retained is a measure or the equivalent to accumulation of body albumin" (von Noorden). Only as the nitrogen of the food becomes an integral part of cell life (Hoffmeister's stabile protein) is it servicable to the organism. Potentially, it may become of service in the form

of labile protein. With a healthy organism and by suitable food—a minimum of protein and maximum of carbohydrate and fat—the nitrogen exchange would tend to diminish to a point where it would coincide with true nitrogen metabolism. In practice this point is rarely reached, and, if possible, would be of doubtful value (Meltzer). These facts should make us extremely skeptical concerning the utilization of protein by the fever-infected organism—especially in typhoid fever.

METABOLISM DURING FEVER. It is of prime importance, in deciding on a dietary for fever patients, to recognize certain altered metabolic processes and thereby adjust the supply to the requirement.

The Causation of Fever During Infection. Increased oxidation brought about through the action of toxins on thermo-regulating centres in the central nervous system is usually given as the cause of fever. Inquiry into the respiratory quotient, heat elimination, and the condition of the circulation bear out this conception only with modification. Von Noorden measured the daily calorie output of a typhoid patient weighing 48 kilograms, the fever ranging about 38.5° C., and found that he eliminated 1200 calories, or 25 per kilogram. The patient preserved his weight on a diet rather rich in protein. No relation has been established between the degree of pyrexia and perceptible alterations in the respiratory quotient. There may be an increase in oxidation processes, but in a large majority of cases the respiratory quotient and caloric output remain normal.[8] The character of ingested food seems to have more influence than any other factor.

The maintenance of body temperature during muscular work and increased oxidation depends on loss of heat through conduction and radiation, and secondly by evaporation of water, mainly through the skin and to a less extent through the expired air. Conduction and radiation are limited by circulatory changes in infective fever. This action begins as soon as the absorption of toxins commences by causing a general constriction of ultimate arterioles. Heat production and heat outgo become equal after the first thirty-six hours, with the body temperature at a higher level.

It seems probable that some degree of pyrexia in typhoid fever may be accounted for by oxidation processes in the intestine due to bacterial activity, especially in cases in which the food content is favorable for such action. Thermogenic bacteria are common inhabitants of the bowel (Macfadyen).[9]

Increased Protein Destruction in Fever. An increased destruction of cellular protein which shows itself in urinary nitrogen is always noted in infective fever. This loss is attributable to the

[8] Increased oxidation is always noted during the initial rise of temperature.

[9] Jour. Path. and Bact., 1895, iii, 87. (Full references to French literature.)

cause of the fever or the infective process, and the loss does not account for the increased pyrexia. In a case observed by von Leyden and Klemperer, the diet contained 25.1 grams of nitrogen in twenty-four hours and the excreta contained 31.5 grams, of which 29.6 grams appeared in the urine. On the observed day the patient received a total of 1732 calories, and the highest temperature was 40.2° C. There was a nitrogen loss of 6.4 grams. The cause of such losses may be found in two directions: (1) Destruction due to the rise of body temperature. This is shown best by the loss of nitrogen in animals subjected to a high temperature. Voit found that by artificially raising the temperature of a fasting dog to 40° for a period of twelve hours, there was an increase in nitrogen elimination of 37 per cent. above the normal. There was no toxic element to obscure the picture. (2) Nitrogen loss due to the virulence with which the toxins attack body tissue. This varies with the character of the infection. According to Ehrlich, the labile protein molecule and the toxin molecule both contain haptophore groups, and the mechanism of attachment to cellular protein is the same. During infection, cellular protein exhibits greater affinity for toxins than labile (food) protein. If this were not so, immunity processes would be seriously inhibited. Therefore, in severe infection, with abundance of toxins in the circulating blood, cellular activity results in augmented nitrogen output. Regeneration is possible only as the intoxication decreases and attachment of nutrition nitrogen supercedes that of toxin nitrogen. It will be possible to maintain cell equilibrium of nitrogen only when side-chains available for nutrition are equal in number to those combining with intermediary bodies. If the former exceed the latter as the infective process subsides, cell regeneration takes place and the effect is retention of nitrogen in the form of stabile protein.

Metabolism of Fats and Carbohydrates in Fever. In pyrexia the glycogen of the liver disappears and that of the muscles increases. This migration is probably accounted for by the need of the cells for combustible material. The burning of body fat is proportional to the burning of protein, and plays its part in the weight decrease. After absorption the behavior of carbohydrates is not materially different from that in health.

The Acidosis of Pyrexia. An increase in the output of urinary ammonia (in combination with acid) has been noted. This may reach as high as 6 grams (normal 0.7 gram). The three acetone bodies have been isolated, and feeding starch does not always cause them to disappear. Von Noorden was inclined to attribute their appearance to inanition and lack of nourishment. They certainly indicate perversions in oxidation power. It is interesting to note in this connection that Herter has isolated small amounts of acetone from cultures of mixed fecal bacteria. Since it has been shown that the acidosis of diabetes is not dependent on bacterial activity

in the intestine, too little importance has been attached to a possible connection. Kraus is of the opinion that determination of the acidity of the urine is of little value. There is a type of acidosis which reveals itself by hyperacid urine, decrease in salivary alkalinity, and possible hyperchlorhydria. Some symptoms of this type accompany fever. Whether the acidity can be referred to destruction of body or food protein[10] cannot be said.

The Internal Organs in Fever. While in many instances the functional capacity of an organ can be conjectured by postmortem changes, urinary evidences of decrease in renal function are too well understood to need more than passing mention. It must be granted that these organs bear the brunt of the infection and are most susceptible to its influence. The hepatic changes also have been mentioned. As to the condition of the glands having internal secretion, but little is known. It would be a most curious confirmation of clinical observation if it could be shown that vasomotor dilatation so characteristic of certain infections depended on failure of the adrenal gland.

The Specific Dynamic Action of Foodstuffs. Many years ago, Rubner recommended that the excessive use of protein in infective fever was contra-indicated by its specific dynamic action. This is best illustrated by experiment on a starving dog. The heat produced was observed to rise 42 to 46 per cent. after consumption of 2000 grams of meat. At the height of digestion, the increase was still greater, sometimes attaining 90 per cent. The effect passed off at the close of the tenth hour. As long as the protein consumption remains high, the energy transformation remains high. According to Rubner, for every 1 per cent. addition to the protein of the food, there is an increase in the consumption of energy on a pure meat diet of from 2 to 2.5 per cent.[11] The constant deposit of protein continually raises the heat production in the organism until a point is reached when no more protein is added to the body.[12] This is the point of nitrogen equilibrium, and when the sparing action of fats and carbohydrates is utilized, the point is quickly attained. It is evident that on a purely protein diet the dynamic needs cannot be met, the same conditions obtaining in a less degree by a use of a relative excess of protein. The only exception to this rule is when the intake of protein is less than the dynamic needs of the starving organism at rest. This increase in energy con-

[10] The proportion of bases to acids in the protein molecule averages 25 to 35. Mann's Chemistry of Proteins.

[11] It is usually calculated that 20 per cent. increase in the dynamic value of food for fever patients should be allowed over that of the resting individual. It would be interesting if it should transpire that this resulted solely from protein consumption.

[12] We are not at liberty to use the terms "heat equilibrium" and "nitrogen equilibrium" as synonymous terms. There may be loss of weight with nitrogen retention. There may be heat equilibrium with loss of nitrogen. To assume that an individual is in heat equilibrium because there is a nitrogen balance or gain would not be allowable until weight had been maintained for a long period.

sumption is manifested by increases in oxidation and consequently is manifested in the respiratory quotient. This specific dynamic factor which averages in the case of protein 30.9 per cent. has been found to be 12.7 per cent. for fat and 5.8 per cent. for sugar, carbohydrates in general falling between the last two figures. With respect to fats and carbohydrates, this increase in energy consumption has been referred to increased activity of digestive glands, but for proteins it is attributable to the specific action which protein has upon oxidation processes in the cell.[13] Magnus-Levy has shown that the effect is not produced by meat extractives, while Lusk, basing his opinion on Mandel's work, is inclined to attribute it to the uric acid group.

Svensen's work in general, shows that the same principles apply to the typhoid fever patient, finding an increase in gaseous exchange after meals.

Sources of Corporate Energy. The caloric values of protein, carbohydrate, and fat are well understood. The point to be especially elucidated involves the source of energy in protein. The amount is relatively small, and there is good reason to believe that it can be referred to its carbohydrate content or to carbohydrate derivatives. Pavy has shown that nearly all proteins contain a carbohydrate group preformed in the molecule. This may attain 10 per cent. It is quite possible that the transformation of sugar from protein may determine the available source of energy in protein. Lusk, also, has shown that 52.5 per cent. of the energy contained in meat protein may be liberated under certain circumstances as dextrose in the organism, and this directly used by the cells. Protein as a source of energy is, therefore, not as economical as carbohydrate or fats, the organism being unable to maintain heat production by its use without the assistance of more easily combustible foodstuffs.

The Standard Fever Diet. The ideal fever diet should consist of such foodstuffs as will meet the dynamic needs of the organism, and prevent excessive loss of weight until natural immunity processes terminate the disease. Its specific dynamic action should be as small as possible, and the end-products of metabolism should be such as to be capable of elimination without additional strain to those organs. If, by reason of digestive limitations, the food is subjected to bacterial influences, the end-products of such alteration should present the minimum of toxicity. Of considerable importance is the danger of increasing the relative acidosis through improper food, or possibly augmenting the fever through excessive use of purins.

The objections to protein as a foodstuff for the typhoid fever patient having been pointed out, it remains to show that, as compared with probable damage, very little good follows its use. To maintain

[13] To illustrate this point, an exact comparison between the patient with fever and an individual subjected to high external temperature is allowable.

the body in nitrogen equilibrium does not prove that protein reaches the cell and becomes a part of intracellular life. In fever there are many influences which may turn it aside from its normal pathway. Nitrogen metabolism in pyrexia cannot be altered to the normal as long as the infective process continues, the toxic destruction of the cell strictly limiting regeneration even with a large protein intake. In the latter event the nitrogen exchange is raised, and the toxic destruction of cellular protein continues. Nitrogen loss in infectious diseases is the inevitable consequence of the disease, and while not desirable if it can be prevented, still it is yet to be shown that its loss is *per se* objectionable.[14] In any event, if the sparing action of fats and carbohydrates is used to the fullest extent compatible with appetite and digestive capacity, it is probable that this deprivation of protein food will not figure in the death rate.

Voit has shown that carbohydrate may spare the loss of body albumin from overheating by subjecting a starving dog (the same dog!) whose temperature had been raised to 41° C. for a period of twelve hours and noting that 40 grams of cane sugar protected against nitrogen loss. The toxic element was not present in this experiment, and the loss due to pyrexia alone was compensated. The starving nitrogenous metabolism can be reduced to one-third by the use of carbohydrates (Folin, Rubner). Siven maintained nitrogen balance in a man weighing 65 kilograms on 4 or 5 grams of nitrogen daily. Three and a half per cent. of the total caloric value of the food was in protein, the total being 2717. Chittenden found that nitrogen equilibrium could be maintained on a diet the caloric value of which was from 1500 to 1600. The first few days of Cetti's starvation shows that 13 per cent. of the total energy exchange was derived from protein and 87 per cent. (minus a small fraction derived from glycogen) from fat.

Von Noorden measured the daily caloric output of a number of fever patients. One suffering from typhoid fever yielded only 23 to 25 per kilogram of body weight. With lower values, weight was maintained by retention of water, as shown in many cases by developing œdema. Lower values sometimes were obtained in chronic fever, showing that prolonged intoxication of the cell was followed by low oxidizing power. This corresponds very well with the minimal caloric output of the resting healthy man as determined by Johanssen and others, the gaseous exchange remaining low. To this figure should be added sufficient to equalize the loss from the specific dynamic action of the foodstuff used, which in the case of carbohydrates and fats averages about 8 per cent. Von Leyden's estimate of caloric necessities for the bed-ridden patient, in diseases not involving metabolic perversions, was from 28 to 30 calories per kilogram.

[14] Concerning the condition of the cardiac muscle, the loss of tone in febrile states is probably due to overwork and toxic destruction, loss from pyrexia not entering as a factor.

These figures are given to furnish a suitable basis for computing the average needs of the patient suffering from typhoid fever. The advantage of arbitrarily establishing a standard for every patient is doubtful, even on a basis of weight. The practising physician recognizes that while the science of physics requires the use of precision instruments and takes cognizance of minute differences, it is not possible to proceed with such exactitude where vital forces are concerned. The totality of factors influencing cell activity is not yet apparent.

The Use of Plain or Fermented Milk in Fever. There are many disadvantages in the use of milk referable to its chemical composition. According to Dreschel, 9 per cent. of the nitrogen in casein can be separated directly by hydrolytic splitting into urea, this portion being of little service to the organism. The casein molecule contains 7 per cent. tyrosine and 1.5 per cent. tryptophane which under the influence of bacteria yield toxic phenol and indol compounds It contains no glycocol.[15] To the chemist, casein is easily disintegrated, for it contains no peptones of the antigroup. Its use in practice demonstrates that when caseinogen is converted to casein by the action of lime salts, large curds form in the stomach and intestines, limiting the action of enzymes to the exterior surface, while bacterial processes continue on the interior. Sassetzky found that the loss of nitrogen on a milk diet in typhus ranged as high as 24 per cent. The absence of curds from the stools does not demonstrate the utilization of the casein molecule, sufficient time elapsing while traversing the gastro-intestinal tract to allow of bacterial disintegration. Impure, it adds infection to the intestinal contents.[16] It also furnishes excellent culture media for typhoid and other bacteria.

Rubner[17] says: "To cover a requirement of 2400 calories daily, 3410 grams of milk would be needed, which contains 140 grams protein!" This is more than twice the amount of protein contained in Chittenden's dietary for the normal men. It holds preformed in its molecule, carbon nuclei which are capable of great evil and does not contain those which are obviously of the most service.

The Use of Alcohol as a Stimulant. The caloric value of alcohol (72 grams equals 500 calories) makes it appear attractive as a stimulant. It is rarely if ever that the condition of the circulation calls for its use, viz., high peripheral pressure with failing cardiac tone. The opposite usually obtains. Recent work on the pharmacology of alcohol raises a very grave doubt as to whether it is ever beneficial.

[15] The chemical relationship between glycogen which disappears from the liver during fever and glycocol indicates that an abundance of the latter would be advantageous.

[16] The pediatrists recognize the value of bacteria-free food. Incidentally it might be added that cow's milk was originally intended for growing calves.

[17] Von Leyden's Handbuch, 1903, i, 132.

In closing, nothing better can be said than to quote the following spoken by Dr. Alexander Lambert[18] at a recent meeting of the American Medical Association: "I think if Dr. McCrea will leave out milk, he will be convinced that there is a better diet and a more generous one of rice, broth, sugar, butter, and a few crackers. It will open his eyes to the possibilities of a diminution in the toxicity of typhoid fever, a diminution of the delerium and meteorism in a majority of patients."

Sample Diet—Typhoid Fever.

Approximate values are based on the following data: Body weight, 60 kilograms; total caloric value, 2300; per kilogram body weight, 35 calories; distribution by weight, protein, 5.3 per cent.; carbohydrate, 55.5 per cent.; fat, 4.5 per cent. (Balance ash, water, and inedible refuse. This will yield 0.85 gram of nitrogen.)

Hour.	Material.	Weight.	Approximate amount.	Percentage.			Calories.
				Protein.	Fat.	Carbohyd'te	
		Grams					
6 A.M.	Choice of: toast,	..	2 thin slices				
	Huntley and Palmer breakfast biscuit, or	35	5				
	Zwiebach	..	3	8.9	1.4	60.3	125
	Cup coffee, sugar	24	2 heaping teaspoonfuls	..	..	100.0	100
	Cream	8	1 dessertspoonful	2.4	17.6	4.5	35
8 A.M.	Gruel, cream of wheat	60	2 heaping tablespoonfuls	9.3	1.6	74.0	230
	Oyster crackers	30	Large handful	7.6	8.2	71.6	130
10 A.M.	Vegetable soup	250	8 ounces	*6.3	Negligible	43.9	190
12 M.	Baked potato	80	Size of orange	1.9	1.0	20.0	65
	Creamed after mashing	16	1 tablespoonful	2.4	17.6	4.5	35
	Butter	8	Size of a domino	1.0	80.8	..	60
	Hot weak tea, sugar	24	2 heaping teaspoonfuls	..	..	100.0	100
	Toast	35	2 thin slices	8.9	1.4	60.3	125
2 P.M.	Tapioca pudding	60	2 tablespoonfuls	2.8	2.9	28.2	100
	Oyster crackers	30	Large handful	7.6	8.2	71.6	130
4 P.M.	Rice	100	.....	6.5	0.3	76.9	350
	Butter	8	Size of domino	1.0	80.8	..	60
	Sugar	24	2 heaping teaspoonfuls	..	..	100.0	100
6 P.M.	Toast	35	2 thin slices	8.9	1.4	60.3	125
	Butter	8	Size of domino	1.0	80.8	..	60
	Sugar	12	1 heaping teaspoonful	..	..	100.0	50
8 P.M.	Vegetable soup	250	8 ounces	6.3	Neg.	43.9	190
	Oyster crackers	30	Large handful	7.6	8.2	71.6	130

* Percentage of solid material.

Weights of vegetables are those prior to cooking. Butter washed to remove free acid is preferred. All foods to be thoroughly cooked; four hours for vegetables other than potato.

[18] Discussion, Jour. Amer. Med. Assoc., 1908, li, 987.

The Preparation of Vegetable Soup. Sixty grams each of green or canned French peas, white dry beans, potato, rice, and noodles, and 15 grams of carrot are boiled in water at least four hours. Sufficient water should be added to make one liter—which is sufficient for four feedings. The whole yields 760 calories, of which 6.3 per cent. is protein, fat less than 0.2 per cent., and 43.9 per cent. is carbohydrate. When ready to use, stir up sediment and allow the patient to eat all (including noodles), with the exception of the pea and the bean skins. Onion may be added for flavor if desired.

General Directions for Feeding. The patient should be fed with a spoon by the nurse.

The food should remain in the mouth as long as convenient.

Allow water between feedings, not at feedings.

Allowances or corrections are to be made for increase of nitrogen need during the first ten days and during convalescence. At the height of fever, if the patient cannot eat the full quantity, substitute isodynamic quantities of milk sugar. A relative decrease of weight should be reflected in the caloric value of the food on the basis of 4 kilograms of loss per week of disease.

THE THERAPEUTIC USE OF BACTERIAL VACCINES.

WITH THE REPORT OF CASES.

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This study does not comprehend a discussion of the various theories of immunity, but is a description of the technique employed in making vaccines, with clinical observations on eight cases in which vaccines were employed.

Technique. The technique followed was as simple as routine bacteriological work permitted. The preliminary step was the securing of cultures, either from the blood or pus, and determining the organism that produced the infection. In cases in which a general infection seemed to exist, blood cultures were first tried. If these were negative, then the organism was secured from the seat of local infection.

In cases of localized infection cultures from the pus as well as blood cultures were taken, in order that no unnecessary time might be lost. If blood cultures are positive, it is preferable to make the vaccine from that source, as one is then certain of the infecting organism; whereas cultures from pus are often mixed growths, and much valuable time is lost in plating for pure cultures. Besides

one is not sure which of the germs in the mixed culture is the organism doing the damage.

After the germ had been properly identified and a pure culture grown for eighteen to twenty-four hours on some solid media, such as plain or glycerin agar, the germs were scraped off and mixed with sterile normal salt solution, making an even emulsion. This emulsion was then standardized; that is, the number of germs per cubic centimeter of vaccine was determined by Wright's method. The emulsion was then placed in a hot box, kept at a uniform temperature of 65° C., and allowed to remain there for thirty minutes. After adding a capillary drop of lysol to each 10 c.c. of the emulsion and placing a sterile rubber cap over the neck of the bottle, the vaccine was placed in a refrigerator, and so kept except when using.

This technique is not difficult to master, and need not necessarily be confined to expert laboratory workers. The most difficult part of the process is the determination and isolation of the infecting germ. Care must be taken that spore-bearing germs are not present, as the temperature to which the vaccine is submitted will not kill spores. One may be assured that the vaccine is sterile by planting it on agar and incubating for twenty-four hours. If there is no growth, one is fairly sure that no spore forms or living organisms are present of the aërobic variety; anaërobes, such as tetanus and gas-producing bacilli should be searched for in smears; the clinical symptoms of the patient will suggest the necessity of anaërobic cultures.

The cases to be discussed are divided into two groups:

Group I. Those in which the organisms were demonstrated in the blood. Under this three forms of infection are presented: (*a*) Puerperal septicemia; organism, Streptococcus. (*b*) Septicemia following otitis media; organism, Streptococcus. (*c*) Septicemia accompanying ulcerative endocarditis; organism, Staphylococcus pyogenes aureus.

Group II. Those in which the organisms were not found in the blood. Under this five different infections are represented, general and local processes: (*a*) Appendicitis, complicated by pyemia and liver abscess; organism, Bacillus mucosus capsulatus. (*b*) Appendicitis, complicated by pyemia; organism, Streptococcus. (*c*) Puerperal fever, streptococcic endometritis. (*d*) Pelvic cellulitis, abscess in the cul-de-sac; organism, Bacillus coli communis. (*e*) Infection of the foot followed by cellulitis of the leg, complicated by erysipelas; organism, Streptococcus.

No attempt was made in these cases to limit the patient to vaccine treatment only. In every case the usual routine surgical or medical treatment was carried on, irrespective of the vaccine inoculations. It cannot, therefore, be said that the vaccine treatment was partly or entirely responsible for the cure. It was not the purpose of this paper to prove that vaccines only effected the cure, but rather to present the cases in such a manner as to encourage the use of vaccines

as an adjunct to medical and surgical procedures in certain types of infections which up until now have stubbornly resisted all curative measures.

GROUP I, Case I.—*Puerperal septicemia of forty days' duration; streptococci isolated from the blood; vaccine inoculations given; the temperature came to normal in two days; no further chills.*

Six weeks before admission the patient had been delivered at term of a healthy child. Fever set in immediately and ran a septic course. The patient had daily chills lasting from a half to one hour. During this six weeks the usual routine treatment was followed. She gradually lost her strength; but bedsores developed, the hemaglobin fell to 25 per cent. and the red cells to 1,000,000, and food could not be retained. There was considerable abdominal distention. In this seemingly hopeless condition vaccines were tried.

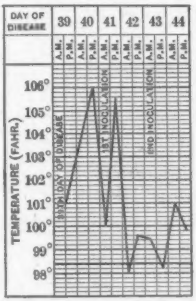

FIG. 1.—Temperature chart of Case I. Puerperal septicemia; streptococci isolated from the blood; autogenous vaccine used.

Streptococci having been isolated in pure culture from the blood, a vaccine was made, and 50,000,000 bacteria were inoculated on the fortieth day of septic fever. In two days the temperature had fallen to normal (Fig. 1), the chills stopped, and there was an immediate change for the better. The inoculations were repeated every third day, increasing 25,000,000 each dose, until six doses had been given. While the temperature had been lowered and the chills stopped, the patient's vitality was so depressed (the hemoglobin having fallen to 18 per cent.) that she would not respond to supportive measures, and died from inanition. In the light of more recent experience it would seem to me that the doses given were too large and may have contributed to the depression present.

GROUP I, Case II.—*Bacteremia following mastoid disease; streptococci isolated from the blood; treatment by autogenous vaccine and operation; recovery.*

A boy, aged seven years, came into St. Mary's Hospital with the following history: Two weeks previously he began to complain of

general malaise and headache, which lasted a full week. There was no chill; no nosebleed; but there was loss of weight, increasing weakness, and some night sweats. He was feverish at night. There was some earache in the right ear, but no discharge. (Later, the mother said the boy had been complaining of more or less earache for six weeks.) Physical examination showed a poorly nourished, fairly well-developed young boy. The left ear appeared normal. The right ear was reddened, and the drum seemed covered with a small amount of exudate; but was not bulging. The external auditory canal seemed smaller than the left. The chest, lungs, heart, abdomen, and extremities were negative. On admission the temperature was 103.6°; pulse, 105; the respirations, 40. For the next ten days the temperature was of a septic type (Fig. 2), reaching as high as 105.4° on several afternoons and going to normal or subnormal in the forenoon. The pulse was rarely below 110, and several times as high as 128. On the second day after admission the right ear

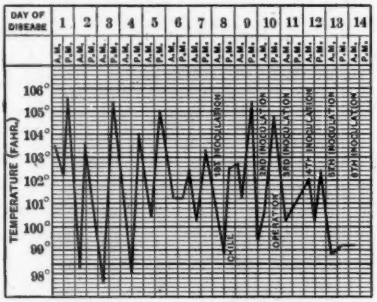

FIG. 2.—Temperature chart of Case II, showing the relation of the temperature to vaccine inoculations and operation. A case of mastoiditis; streptococci isolated from the blood.

drum was punctured and bloody serum escaped. Discharge during the next eight days was very scanty. On the fifth day the patient complained of pain in the left elbow and both knee-joints, which were slightly tender and swollen. On the sixth day after admission blood cultures were positive for streptococci. On same day tenderness was made out over the spleen and an endocardial murmur was heard, and two days later swelling was noticed in the subparotid region. The posterior lymph chain showed enlarged, discrete nodes, somewhat tender, but no fluctuation. The swelling in the parotid region rapidly increased, and operation for mastoiditis and sinus thrombosis was performed on the tenth day after admission. The mastoid was found but very little, if at all, involved, and on opening the sinus, a small amount of chocolate-colored material was removed. Cultures were taken, both from the mastoid cells and from the sinus, but were negative. Several glands from the posterior chain were removed

and found to be acutely inflamed. Two days after operation blood culture was negative.

On the seventh day after admission autogenous vaccine was administered, the initial dose being 17,500,000. Forty-eight hours later a second inoculation of 50,000,000 was given. At this point the operations above referred to were performed. On the three days following operation small daily doses of 5,000,000 streptococci were inoculated. On the fourth day after operation the temperature came to normal and remained practically so, and the patient made a perfect recovery. The fact that the organisms were absent from the blood two days after operation suggests that the infection of the blood stream was transient, as occurs early in pneumonia and typhoid fever, and that the case was a bacteremia rather than a septicemia, and this is further suggested by the immediate recovery after operation.

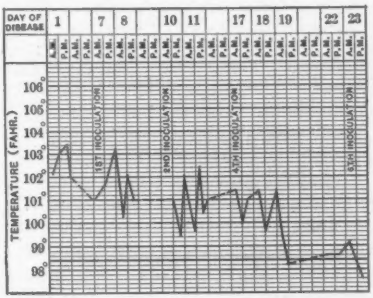

FIG. 3.—Temperature chart of Case III. Ulcerative endocarditis.

GROUP I, Case III.—*Ulcerative endocarditis, pericarditis, and pleurisy with effusion; staphylococci isolated from the blood; vaccine inoculations resulted in these processes clearing up; for one month marked improvement took place, when the patient contracted lobar pneumonia and died.*

Two weeks before admission a boy, aged sixteen years, commenced to have severe pains in the lumbar regions. He lost his appetite and became constipated, and finally had to give up work. He felt considerable palpitation, and was short of breath on exertion. His feet had been swollen for some time. Physical examination was negative, except the heart, which showed the apex beat in the sixth space, three and three-fourth inches from the midline, heaving and forceful; a systolic and a diastolic murmur over the aortic area; a presystolic thrill at the apex; the first sound at the apex, booming preceded by a short rumble; the systolic murmur at base transmitted downward and heard at the apex, but not transmitted to axilla, and a pericardial, to-and-fro friction. Five days after admis-

sion a blood culture was taken, and Staphylococcus pyogenes aureus was isolated, and a vaccine was made.

The leukocytes, on admission, were 18,000; the polymorphonuclears, 91 per cent.; large mononuclears, 4.5 per cent.; lymphocytes, 3 per cent.; eosinophiles, 0.8 per cent.; basophiles, 0.7 per cent. Fifteen days later the leukocytes were 50,000; the polymorphonuclears, 80 per cent.; large mononuclears, 14 per cent.; lymphocytes, 6 per cent. On the tenth day after admission the chest was aspirated and fluid obtained. Two days later signs of fluid in the pericardium were made out. The pericardium was aspirated, and over an ounce of clear fluid was obtained. During this period the heart action was very labored, and the pulse reached 132 per minute and was very feeble.

The first inoculation of vaccine was given on the seventh day after admission, and inoculations were given twice a week thereafter, until six had been given. The dosage was as follows:

First inoculation	208,000,000
Second inoculation	312,000,000
Third inoculation	416,000,000
Fourth inoculation	520,000,000
Fifth inoculation	624,000,000
Sixth inoculation	725,000,000

During the first two weeks of vaccine treatment the patient grew gradually worse. During the third week, however, his condition improved and his temperature gradually became normal (Fig. 3). His pulse, which had ranged between 110 and 130, became about 80, and the respirations, which had varied between 35 and 40, decreased to normal. During the third week of treatment his whole appearance changed and his strength steadily increased. After nearly four weeks of normal temperature, during which time marked improvement had taken place in his general condition, he contracted pneumonia and died.

GROUP II, Case IV.—*Pyemia following appendicitis; liver abscess; blood cultures negative; Bacillus mucosus capsulatus isolated from the pus on the fortieth day after operation; the use of vaccines made from this organism was followed by gradual fall of the temperature to normal and perfect recovery.*

J. E., aged forty-six years, came to operation for appendicitis after the usual symptoms. The appendix was found to be gangrenous. Behind the cecum was a small abscess. The appendix was removed, the abscess evacuated, and drainage inserted. The temperature did not rise above 101° on the three days following the operation, but chills, which had preceded the operation, continued and became more prolonged. The two weeks following operation showed a temperature septic in type and the patient's condition grew gradually worse. The wound was kept open and drainage seemed ample during this period. No enlarged liver could be made

out, though the patient became slightly jaundiced during the second week after operation, and occasionally complained of pain in the liver region. No further surgical measures seemed of use, and resort was had to intravenous injections of collargolum, and inunctions of Credé's ointment were given. These measures did not seem to affect favorably the course of the disease. Stock vaccines and antistreptococcic serum were used, with absolutely no results. The patient was in extremis. Blood cultures were entirely negative. A marked grade of secondary anemia was present, the red blood cells being 2,712,000. At this point an autogenous vaccine was made from cultures of Bacillus mucosus capsulatus, which was isolated from the pus of the appendix wound.

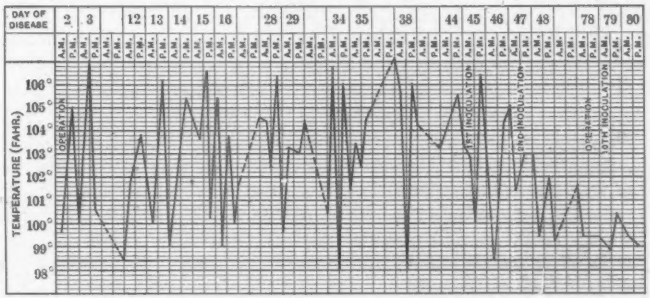

FIG. 4.—Temperature chart of Case IV, showing the temperature curve before and after inoculation. A case of pyemia with liver abscess following an appendix operation.

The first inoculation of the autogenous vaccine was made on the forty-fifth day after operation; thereafter two inoculations each week were made, with doses as follows:

First inoculation	40,000,000
Second inoculation	50,000,000
Third inoculation	50,000,000
Fourth inoculation	50,000,000
Fifth inoculation	55,000,000
Sixth inoculation	55,000,000
Seventh inoculation	70,000,000
Eighth inoculation	70,000,000
Ninth inoculation	110,000,000
Tenth inoculation	110,000,000
Eleventh inoculation	110,000,000

Inoculations were then given weekly for a month at the same dosage, viz., 110,000,000.

After the first inoculation there was a slight fall in temperature (Fig. 4). After the second there was a decided fall. Chills, which had occurred regularly every day for forty-five days, ceased. The patient's general condition improved. The temperature remained between 99° and 102° for a month after inoculations began, during

which time signs of a liver abscess became evident. The abscess was opened and drained. Bacillus mucosus capsulatus was found in the pus from this abscess also. The temperature came gradually to normal after the abscess was opened, and the patient made a perfect recovery. Nearly one year later he reports himself in perfect health.

GROUP II, Case V.—*Postappendicular pyemia; abscess in the shoulder-joint; vaccine made from the pus; improvement after the second inoculation; perfect recovery.*

M. M., a woman, aged thirty years, was taken ill, eight days before admission, with the symptoms of appendicitis. At an operation performed immediately the appendix, perforated and gangrenous, was found enclosed in an abscess cavity, well walled off. Drainage was inserted and wound left open. The temperature for the first day after operation did not rise above

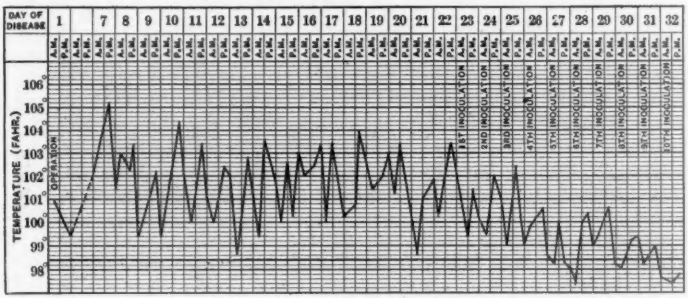

FIG. 5.—Temperature chart of Case V; postappendicular pyemia. The temperature curve before and after inoculations.

99.5°, but on the days following rose each afternoon and became septic in type. Five days after operation the wound was explored, but no pus pockets were made out; the abdomen was not rigid, and there were no signs of general peritonitis. On the ninth day after operation the left shoulder-joint was very painful, considerably swollen, and markedly tender. This continued until the seventeenth day after operation, when joint was aspirated and a seropurulent fluid obtained. Cultures from this fluid yielded a pure growth of streptococci. Several blood cultures were taken, none of which were positive. On the twentieth day after operation the right sterno-clavicular joint became swollen, tender, and slightly reddened, and the overlying tissue reddened. The leukocyte count on admission was 33,000; 89 per cent. polymorphonuclears; five days after admission, 33,300; 93 per cent. polynuclears.

On the twenty-second day after operation the first inoculation of autogenous streptococcic vaccine was given, the dose being 2,500,000. This was repeated daily until twelve inoculations had been given.

The temperature gradually came to normal (Fig. 5); her general condition improved from the first inoculation; the joint symptoms gradually disappeared, and the patient made a complete recovery. After the vaccine treatment was begun, all surgical and other medical measures were omitted. At the time inoculations were begun the patient was in a very critical condition.

GROUP II, Case VI.—*Puerperal fever, developing on the sixth day of the puerperium; blood culture negative; intra-uterine culture showed streptococci; stock streptococcic vaccine from a streptococcic septicemia was given, and the temperature came to normal, but rose on the second day; autogenous vaccine was then given, and the pulse, temperature, and respirations came to normal.*

A woman, aged thirty years, was delivered of a child at full term. For five days after delivery the temperature was normal; the uterus was contracted and the patient seemed to be doing well. On the sixth day the temperature suddenly rose to 105° in the morning

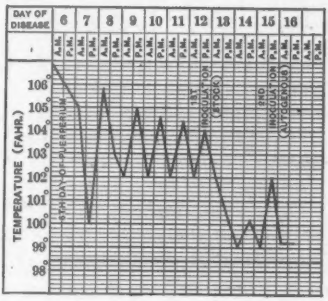

FIG. 6.—Temperature chart of Case VI; puerperal fever.

and dropped to normal in the afternoon. The next day it rose in the morning to 105.4° and fell in the afternoon (Fig. 6). The patient exhibited the usual symptoms of septic infection—rather drawn facies, rapid respiration, rapid pulse, extreme restlessness. On the sixth day of this septic infection blood cultures were taken, and no growth resulted. Cultures were taken at the same time from the uterine cavity. The cervix was patulous and considerable discharge was present. The intra-uterine cultures yielded a pure streptococcic growth, and a vaccine was made from this.

At the time the culture was taken, 50,000,000 stock streptococci were inoculated. (This strain of streptococcus was obtained from a blood culture taken from a previous case of puerperal septicemia.) The temperature came to normal the next day. Later it rose again, and on the third day the autogenous vaccine was inoculated, the dose being 100,000,000. The temperature again came to normal, being the twelfth day of the puerperium, and was followed by the

pulse and respiration. The patient had no further fever during the puerperium, and made a complete recovery.

GROUP II, Case VII.—*Pelvic abscess; Bacillus coli communis was isolated from the pus; after many autogenous inoculations the temperature came to normal.*

Two weeks before admission, after working hard, the patient began to flow, many clots coming away. This gradually increased and she became very weak. She had high fever at times, chills and sweats for three days preceding admission, and severe pain in the pelvis. Physical examination showed the abdomen to be slightly tender and rigid. The pelvis was tender on both sides, and over the

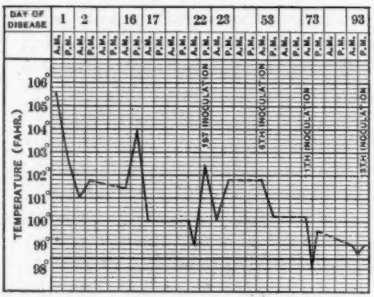

FIG. 7.—Temperature chart of Case VII, pelvic abscess. Bacillus coli infection.

uterus very rigid. The cervix was patulous. A large mass was made out filling the entire cul-de-sac, and very tender on palpation. An operation was made in the cul-de-sac and a large amount of pus evacuated. The fever continued, although drainage seemed ample.

The first inoculation was given on the twenty-second day of the disease. Thereafter inoculations were given twice a week, with dosage as follows:

First inoculation	25,000,000
Second inoculation	50,000,000
Third inoculation	50,000,000
Fourth inoculation	50,000,000
Fifth inoculation	75,000,000
Sixth inoculation	75,000,000
Seventh inoculation	100,000,000
Eighth, ninth, tenth, eleventh inoculations	100,000,000
Twelfth inoculation	150,000,000
Thirteenth inoculation	200,000,000

The temperature came gradually to normal and no further abscesses were formed in the pelvis (Fig. 7).

TYPE II, Case VIII.—*Infected foot, followed by cellulitis of the leg and later erysipelas; streptococci were found in the pus from the foot; a stock vaccine was used, and after two inoculations the temperature came to normal.*

A young colored woman, a nurse, acquired an infection of the foot. The wound was opened and drained. Cultures from the pus showed streptococci. The temperature before the operation was 104.8°. The usual wet dressings were applied, but the temperature continued high. Two days after operation the patient complained of the leg being painful and stiff. The next day the edges of the wound appeared discolored, and within a few hours signs of erysipelas appeared, and extended up the leg. These were painted with carbolic acid, followed by alcohol. The leg was greatly swollen and tender, and signs of phlebitis were present. The temperature was continuously high, between 103° and 105°. On the day erysipelas was noted a stock vaccine of streptococci was used, 50,000,000 being the initial dose. This was followed by no apparent result. The temperature and pulse remained persistently high for the next three days, when the second inoculation of 100,000,000 stock

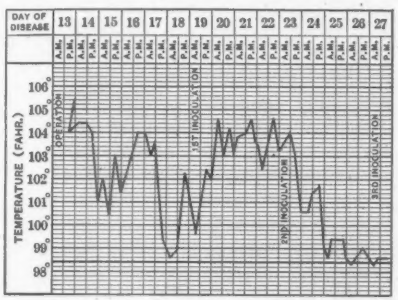
DAY OF DISEASE
13 14 15 16 17 18 19 20 21 22 23 24 25 26 27
A.M. P.M.
TEMPERATURE (FAHR.)
106° 105° 104° 103° 102° 101° 100° 99° 98°
OPERATION
1ST INOCULATION
2ND INOCULATION
3RD INOCULATION

FIG. 8.—Temperature chart of Case VIII; infected foot; erysipelas. Stock vaccine used.

streptococci was given. This was followed by an immediate fall in temperature, the first in ten days, falling to 100.5°. The next day it did not go above 101.4°, and on the following day it came to normal and remained so (Fig. 8). The pulse likewise fell to normal coincident with the temperature, and the patient went on to complete recovery. It should be noted that surgical measures went hand in hand with vaccine treatment, particularly the treatment of the erysipelas with carbolic acid and alcohol painting, and also that the fall in temperature took place about the usual time in the course of erysipelas.

GENERAL SUMMARY. 1. Closely following Wright's method,[1] vaccines were made in eight cases from germs isolated from the blood, when this was possible; otherwise from pus taken from the point of local infection. Two types of vaccines were used—autogenous, and stock vaccine, made from germs secured from sources other than the patient. Of the cases reported, six received autogenous

[1] Transactions of Harvey Society of New York, 1907.

vaccine only; one received, first, stock, then autogenous vaccine; and one received stock vaccine only.

2. The cases reported comprise two of septicemia, one of malignant endocarditis, two of pyemia following appendicular operations, one of puerperal fever, and two of local infection.

3. Classified as to infecting organisms, there were five cases of streptococcic infection, one case of Bacillus coli communis infection, one case of Bacillus mucosus capsulatus infection, and one case of Staphylococcus pyogenes aureus infection.

4. In cases reported, improvement showed itself by a fall in temperature, reduction of pulse rate, and improvement in the general condition. The time taken to bring about these results varied from twenty-four hours to two weeks

5. The number of inoculations given before the temperature came to normal permanently varied with the individual case, from three to seventy-five days, and from two to fifteen inoculations.

6. The number of organisms inoculated as a "dose" varied with the organism given. The following table shows the initial and maximum doses employed:

	Initial.	Maximum.
Streptococcus (3 cases)	50,000,000	100,000,000
Streptococcus (1 case)	50,000,000	200,000,000
Streptococcus (1 case)	2,500,000 (daily)	
Bacillus coli communis	25,000,000	200,000,000
Bacilli mucosus capsulatus . . .	40,000,000	110,000,000
Staphylococcus pyogenes aureus .	200,000,000	725,000,000

In streptococcic infections two methods of dosage were employed, large doses (50,000,000 to 100,000,000) twice a week; or small doses (2,500,000 streptococci) given daily. The latter method gave excellent results in two cases. As a rule, the doses are increased gradually, that is, by one-tenth of the initial dose.

CONCLUSIONS. 1. Bacterial vaccines, if properly used, can do the patient no harm.

2. Autogenous vaccines should be used when possible. Stock vaccines are uncertain, but they may be used when there is delay in securing autogenous vaccines.

3. The technique of preparing vaccines is simple and should be made a part of the routine laboratory work in every well-equipped hospital.

4. Chronic infections yield more readily to the use of vaccines than acute fulminating infections; and local processes are more easily controlled than general infection.

5. If a vaccine is to be of service, it will usually show results within one week or ten days.

Acknowledgment is made of valuable suggestions from articles by W. Gilman Thompson, M.D.,[2] and Drs. Barr, Bell, and Douglas,[3]

[2] AMER. JOUR. MED. SCI., August, 1909.

[3] Lancet, 1907, i. 499.

on the vaccine treatment of septic endocarditis, and Drs. Sutcliffe and Bayly[4] on streptococcic septicemia. I wish to acknowledge also the many useful suggestions of Dr. Thomas W. Hastings.

THE PRESENT STATUS OF TUBERCULIN THERAPY.

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When Koch, in 1890, introduced tuberculin as the long-sought cure for a dreaded disease, he was hailed as a deliverer. But Koch either did not understand his own remedy, or the scientific world misinterpreted his teachings. It is needless to dwell upon the disastrous results following the use of the original "Tuberculin," founded upon the principles of active immunity. It was not understood—large doses were given—and results were in many cases negative—in others fatal. But a few great and far-seeing minds realized that Koch had introduced a remedy which was destined to live. The majority of physicians dropped the new remedy with as much avidity as they had taken it up. Thanks, however, to a few German physicians, led by Koch, and to Trudeau, in this country, work upon tuberculin continued, developed, and improved until a new tuberculin is given us, and a new and better method of administration, with better results and no fatalities. Again the scientific world is inflamed and the pendulum is swinging the other way. Apathy has given way to enthusiasm, and it is well to pause a bit, lest this very enthusiasm lead us to discredit a method which, when used rationally and understandingly, is unquestionably a most valuable aid in the treatment of tuberculosis.

Before a physician is qualified to use tuberculin he should be able to answer satisfactorily four questions: (1) What is tuberculin? (2) What is the theory of its action? (3) What are the various kinds of tuberculin? (4) What is the dosage?

Let me briefly consider the first two questions together, from the theoretical point of view. Arloing and Courmont were the first to discover agglutinins for the tubercle bacillus. Their experiments showing that tubercle bacilli have agglutinating action and that antibodies were present in the blood of a tuberculous patient, were fought by the German observers, denied by Koch and his pupils, in particular Rabbinowitz. Jürgens[1] is of the view that the agglutinins are only an evidence of the presence of soluble tubercle bacillus substances in the circulation. A few years after Arloing

[4] Lancet, 1907, ii, 367.
[1] M. Wolff and H. Mühsam, Deut. med. Woch., 1908, No. 35.

and Courmont[2] came Bordet and Gengou, who presented the complement fixation theory in relation to the tubercle bacillus. Two years ago Wasserman and Bruck, working along the lines of these investigators, demonstrated antibodies in tuberculous tissue, and in the serum of persons treated with tuberculin. They named their antibodies "antituberculin" and thereby conceived a new theory upon which to base the action of tuberculin in the tissues and in the circulation. S. Cohn[3] carried out a series of interesting experiments in attempting to prove or disprove the theory advocated by Wasserman. He examined the blood of 77 patients, and in 10, clinically demonstrated as non-tuberculous, found no antibodies. In 14 "closed" cases of tuberculosis in the first stage he was also unsuccessful in his search. In 53 "open" cases of the second and third stage, 15 had antituberculin in the blood serum. These last named had not been treated with tuberculin, but had developed these antibodies spontaneously. Cohn therefore concludes that antituberculin is not an antitoxin in the true sense, and that the real nature of the Bordet and Gengou antibodies is undetermined—we only know that when tuberculin is introduced into the body it forms a complement (that constituent of the blood which Ehrlich, in his side-chain theory, says eventually destroys the bacteria) with the antibodies. Lüdke[4] demonstrated antituberculin in the blood serum of 17 out of 31 cases treated with tuberculin. Wasserman[5] tries to account for what is known as a tuberculin reaction by the presence of antituberculin in the tissues and for the cessation of a tuberculin reaction by the presence of antituberculin in the blood. Paul Ringer[6] puts this theory in plain English as follows: "The use of tuberculin is based upon the principle of artificial immunity, and any poison in the body has the power of stimulating the system to the production of antibodies." This, in a few words, represents what is considered at the present day the working theories for the action of tuberculin in the tissues and in the blood, namely, the agglutinin theory of Arloing and Courmont, the Bordet and Gengou antibody theory, and the elaboration of the second named, the antituberculin hypothesis of Wasserman and Bruck. It would be useless in the limits of this paper to go too deeply into them. They are extremely interesting, but are at best hypothetical and will no doubt in time be superceded by better and more practical theories. Let me group all theories of this nature together and agree with Tiegerstedt[7] who says that "all changes of immunity are protective adaptations of the body against harmful influences."

In the use of tuberculin our desire is to obtain an overproduction

[2] M. Christian and S. Rosenblatt, Antibodies and Immunity in Tuberculosis, Münch. med. Woch., lv, No. 39

[3] Berl. klin. Woch., xlv, 28.

[4] Münch. med. Woch., 1908, Nos. 16, 15.

[5] Deut. med. Woch., 1906, No. 12.

[6] Jour. Amer. Med. Assoc., 1907, l, 28.

[7] Text-book on Physiology.

of antibodies, call them by whatever technical name one may. We wish to build a defensive armament against which the tubercle bacillus and its ravages will be impotent. An organism can be immunized by injecting more poison into it with increased production of antibodies, that is, active immunization, or we can form antibodies by injecting into the infected individual the blood serum of a previously immunized animal, that is, passive immunization. In tuberculin therapy we aim to produce an active immunization. This immunity to tuberculin is a complete or almost complete tolerance to large doses of tuberculin, the latter dependent upon the judgment of the physician administering the dose, many of our best authorities being satisfied with obtaining even a relative immunity, that is, a tolerance to smaller doses. Hamburger[8] states that artificially acquired immunity to large doses of tuberculin is in many cases merely the result of the inability of the organism to react, due to a complete saturation with antibodies. He describes a test in substantiation of this assertion: A child of twelve months of age was supposed to be immunized but the autopsy showed the contrary. The individual who apparently was immune in reality did not respond to the tuberculin merely through inability to respond to a stimulus. Many physicians in undertaking a course of tuberculin therapy often forget this point. After giving repeated injections and getting no rise of temperature or untoward symptoms, they believe they are getting a state of immunization, when suddenly the patient dies and they find it difficult to account for the failure of the method. Therefore, one will see that this point of inability of the organism to react is of the utmost importance. On the other hand, what is of equal significance is the condition commonly known as a reaction.

Recent scientific investigations by Rosenau and Anderson,[9] Vaughn and Wheeler, and Wasserman and his pupils have done much to clear our ideas upon this question and thus guide us to a more rational and practical administration of tuberculin. Their work upon anaphylaxis or hypersusceptibility has demonstrated that in a tuberculous individual the cells have been already rendered hypersensitive by the action of the tubercle bacillus, and that when the tuberculin has been injected there takes place a division into two groups—poison and non-poison. The sensitized cells bind the poisoned groups and the well-known tuberculin action occurs. In the non-tuberculous individual the condition of anaphylaxis does not exist, and consequently the poison is freed slowly and discharged rapidly without causing any toxic symptoms which are the cause of a tuberculin reaction. The theory of anaphylaxis maintains that when foreign proteins, such as bacterial bodies, are introduced into

[8] Münch. med. Woch., lv, No. 42.
[9] L. S. Mace, California State Jour. Med., vi, No. 9.

the body, certain definite changes occur in the cell by which they are able to break up rapidly a succeeding dose of the same protein. If we accept this theory, then the reason becomes apparent why we should begin tuberculin therapy with minute doses of tuberculin and work up very gradually to the production of a complete, nearly complete, or relative immunity.

Before considering dosage let me review the composition of some of the various kinds of tuberculin on the market, and determine what our choice should be when beginning treatment of a tuberculous case. There are sold to-day between sixty and seventy varieties of tuberculin. Of these, I shall consider the following, the others being either modifications of these or having proved inefficacious:

1. Original tuberculin Koch (O. T.) is a pure culture of tubercle bacilli grown for several weeks in a 5 per cent. glycerin bouillon. This form of tuberculin contains all the soluble secretion products of the tubercle bacillus in a 50 per cent. glycerin solution.

2. New tuberculin (T. R.), introduced by Koch in 1897 to take the place of old tuberculin, the letters standing for tuberculin residue (Ruckstand). Koch having shown that tuberculin was a remedy, but that the great objection to it was its violent reaction, bent all of his energies to the preparation of a substance which should possess immunizing and curative powers, but which would not set up an intense general reaction in tuberculous subjects inoculated with them. Such substances he assumed must be sought in the material of which the tubercle bacillus was composed. After many experiments Koch succeeded in breaking up the bacilli and converting them into a form capable of absorption. For this purpose they were dried and rubbed in an agate mortar in such a manner that no entire particle of tubercle bacillus was left. He extracted all the soluble matter from the tubercle bacilli with distilled water, the resulting solution being T. O. (Tuberculin Obere). The insoluble residue which is separated from T. O., after being converted into a series of solutions, are in turn treated with 50 per cent. glycerin. Substances with only a small toxic effect upon tuberculous individuals are thus precipitated. These residual solutions are the T. R. and contain the whole of the immunizing substances of the tubercle bacillus in a form perfectly capable of absorption. 1 c.c. T. R. is made to contain 0.002 of dried residue. 100 c.c. T. R. is always obtained from 1 gram of dried tubercle bacilli. 1 c.c. of T. R. corresponds to 10 mg. of dried bacilli, but 100 c.c. of T. R. in reality contains only 0.2 gram of dried constituent. 1 c.c., therefore, contains only 0.002 of dry constituent. Ruppel[10] has cleared up a rather erroneous view which had been held for years concerning the amount of dried constituent in 1 c.c. of T. R. It was originally stated that each cubic centimeter contained 10 mg. of solid sub-

[10] Lancet, March 28, 1908.

stance. In reality, each cubic centimeter, as I have shown above, contains but 2 mg. The mistake arose from the fact that 10 mg. of dried bacilli is used to produce 2 mg. of active substance.

3. Bacillen Emulsion (B. E.) is made by using a finely pulverized virulent culture of tubercle bacilli, to one part of which is added 100 parts of distilled water and 100 parts of glycerin. The resulting emulsion contains 5 mg. of dried substance in each cubic centimeter of solution.

4. T. O. (Tuberculin Obere), the solution already described in the preparation of T. R. It is extensively used by some German physicians, but not very much in the United States.

5. Deny's Bouillon Filtre (B. F.) is a filtrate from bouillon cultures from the tubercle bacilli containing all the soluble products in the bacteria. Heat is not used in its preparation.

6. Bovine tuberculin is prepared in the same manner as other tuberculin, except that bovine tubercle bacilli are employed in its preparation.

I have thus far attempted to detail the theory of tuberculin, its action and its reaction, and the principal forms in use at the present time. Some physicians still cling to Koch's original tuberculin (O.T). but in most countries and by the majority of observers it has been discarded for therapeutic use. Koch's New Tuberculin (T. R.) and (B. E.) and the (B. F.) of Denys are the three forms most in use to-day, with bovine tuberculin rapidly gaining popularity. In beginning the treatment of a case of tuberculosis, what should the choice of tuberculin be? I should say any one of the forms mentioned, so long as one is consistent in his dosage and careful in his observation. Most authorities today agree that unheated products act better than heated ones. The unheated products are (T. R.), (B. E.), and (B. F.) and one of these should be our choice. O. T. (original tuberculin) is a heated product. In my own work in the past two years I have used (T. R.) and (T. E.), principally the former, with such good results that I have no intention of discarding it altogether for the (B. E.), as so many are doing.

Among the tuberculins which are well known but not very popular might be mentioned Van Ruck's Watery Extract, Maragliano's Serum, Beranek's Tuberculin and von Behring's Tulase. At the recent International Congress at Washington, Oshijami,[11] of Japan, introduced a new serum called Tuberculo-Toxodin, a chemical preparation from tubercle bacilli applicable to incipient and feverless cases. He claims that his preparation dissolves the tubercle bacilli and transforms the toxic property, thus getting rid of any reaction. Very excellent results are claimed by this observer. Maragliano's serum is considerably used in Italy. Recently Monti,[12]

[11] Jour. Amer. Med. Assoc., xli, Nos. 21, 19, 17, 16, 15.
[12] Gazetta degli ospedali, xxix, No. 2.

of Milan, has reported twenty-five cases of tuberculosis in children treated with it, with especially marked beneficial results in the surgical forms of tuberculosis, the benefit being less marked in the pulmonary forms. On the other hand, the Phipps Institute has experimented with this serum and claims it to be valueless.

The use of the bovine tuberculin is not yet thoroughly understood. In 1901 Koch, at the Congress of Tuberculosis in London, proclaimed the dissimilarity of human and bovine tuberculosis. His view was then challenged and has since been challenged, but he reiterated the same opinion as emphatically as before at the 1908 Congress in Washington. Men like Woodhead, Cohnheim, Aufrecht, Peterson, Ravenel, Arloing and Courmont, Theobald Smith, and Fibiger[13] all challenged Koch at a conference held in camera at this Congress, but the great master would not yield in his view or change his 1901 statement.

Pochin[14] recently reports some observations by which he tried to ascertain whether the action of the opsonins in bovine blood was the same with regard to tubercle bacilli of both human and bovine strain, or whether there was any marked differences which would indicate a distinction between the bacilli with regard to their susceptibility to the action of opsonins and therefore a difference in the resistance of the animal to infection by the bacilli of the different strains. He found marked differences. Without giving his experiments in detail, I quote him as coming to the conclusion that Koch is wrong in the emphatic views he promulgates as to the difference between the human and bovine tuberculosis. A. Cuff[15] reports a case of involvement of the apices of both lungs with cavity formation arrested by injections of bovine tuberculin, giving weekly injections for nine to ten weeks. N. Raw[16] claims that tubercle bacilli of human type produce phthisis pulmonalis, ulcerations of the intestines, and tuberculous laryngitis, and that tubercle bacilli of the bovine type produce tuberculous peritonitis, lymphatic gland tuberculosis, and tuberculous joints. He also believes that the acute miliary form is of bovine origin. Raw believes in giving bovine tuberculin in cases of pulmonary tuberculosis and Koch's T. R. in the surgical forms. He treated eighteen patients having pulmonary lesions with bovine tuberculin, getting very successful results, and 104 cases of surgical tuberculosis with Koch's T. R., with similar effect. He puts forth the hypothesis that the human body is attacked with two varieties of tubercle bacilli which may be present at the same time and which, generally speaking, are antagonistic to each other.

We see, therefore, in studying a subject like tuberculin and in reviewing the literature, how varied and conflicting are the views

[13] Jour. Amer. Med. Assoc., xli, Nos. 21, 19, 17, 16, 15.
[14] Lancet, September 5, 1908.
[15] Brit. Med. Jour., February 15, 1908.
[16] Lancet, February 15, 1908.

of careful observers with large amounts of material at their disposal, and we are unfortunately left very much to our own judgment in the choice of a proper tuberculin. There is as yet no unanimity of opinion.

We come now to the most important chapter of all in the treatment with tuberculin, namely, the dosage, and upon this point the scientific world is rather more in unison. We know that former bad results were mostly due to excessive doses of a serum not understood. I wish to warn against one very common error. Many physicians speak of a dosage of tuberculin in terms of milligrams. We should always stipulate the kind of tuberculin as it is put upon the market, since the amount of essential solid substance in the various forms differ. The beginning dose of tuberculin should always be very small. I believe we owe it principally to Wright that we are today giving proper and efficacious doses of tuberculin. His classical and now well-known work upon opsonins and the opsonic index, which in reality is a determination of the immunizing response of the blood, gave us an exact method of measuring dosage in the administration of tuberculin and gave us a better insight into what constituted a tuberculin reaction and how to avoid it. Although the administration of tuberculin by means of the opsonic index is being rapidly dropped by most observers, owing to the tediousness of its technique and the length of time consumed by the method, still the principle of small and carefully regulated dosage has been taught, and has practically revolutionized tuberculin therapy.

In my own work I have adopted with some slight modifications the dosage recommended by Trudeau.[17] I use T. R., German preparation, and have it put up in dilutions of from 1 to 20,000 to 1 to 10. I begin with 0.2 c.c. of 1 to 20,000 dilution or 0.1 c.c. of 1 to 10,000 dilution the former advocated for convenience, since it is more easily administered in the usual hypodermic syringe. My beginning dose then is 1 to 50,000 mg. of essential solid substance. (Trudeau begins with a dose of $\frac{1}{100000}$ mg.) The initial dose is increased by 0.1 c.c. at intervals of two to three days and sometimes longer, until I am giving 1 c.c. of 1 to 100 dilution. I then increase my interval to a week and begin with 0.1 c.c. of 1 to 10 dilution, and when several doses of this dilution have been given I even extend the interval to two weeks. When I reach the dose of 1 c.c. of 1 to 10 dilution which is 0.1 c.c. of the pure T. R., or $\frac{1}{5}$ mg. solid substance, I keep the patient upon this dose for some weeks. I seldom go beyond this dose, and find it unnecessary to give the patient large doses of the pure tuberculin.

This method has operated efficaciously in my hands in a number of cases, the detailed report of which I shall reserve for a future time when my series of cases shall have reached a sufficiently large number to make comparative deductions.

[17] Amer. Jour. Med. Sci., 1906, cxxxii, 175.

It must be especially understood that a course of tuberculin therapy cannot be hurried. The patient must be told that it will require from six months to one year to accomplish, and the physician must realize the importance of increasing his dose very slowly. Reactions which were originally thought to be a necessary concomitant of tuberculin injections should be avoided. Trudeau has published some very extensive reports upon this subject in the last three years, and he claims that a reaction means that we have exceeded the patient's capacity for responding, and that it can and should be avoided. Denys lays down certain precautions: (1) Do not begin with too large amounts. (2) Do not raise the dose too rapidly or at too short intervals. (3) Do not again inject before all effects of a reaction have passed. (4) After a reaction, begin with a smaller dose than the one which caused the reaction. (5) Do not neglect to consider the patient's symptoms—such as headache, malaise, etc. I cannot improve upon these admonitions promulgated by Denys and adopted by Trudeau, rules which should be memorized and used as a guide by every physician attempting a course of tuberculin therapy. If they are followed, tuberculin can accomplish no harm, even though it may not produce an arrest of the disease.

To carry to a successful issue a course of tuberculin therapy requires careful observation and good judgment. The patient should always rest after an injection, and should never during the treatment overexercise or overstrain. Overexercise is often responsible for a reaction due to auto-inoculation. In fever cases especially the patient should be kept absolutely in bed until the temperature is normal, and then the tuberculin injections should be begun as previously indicated. Latham and Inman[18] advise absolute rest in bed as the only safeguard against auto-inoculation, and stipulate that the dose of tuberculin given must bear a definite relation to the amount of auto-inoculation, either occurring spontaneously, as in the fever cases at rest, or artificially induced, as in the afebrile cases up and about. Therefore, we cannot be too cautious in the conduct of our cases, having always before us the possibility of inoculation from the toxins circulating in the blood. We cannot be too cautious in beginning tuberculin injections nor in taking cognizance of all signs which occur during the treatment, and we must be especially careful to give the patient at all times sufficient rest.

Being sure that our beginning dose is small enough and that we are progressing with proper increase and at proper intervals, avoiding reaction, guarding against auto-inoculation, and never continuing the injections if perchance a reaction has occurred, the question then naturally arises, When should we cease injecting tuberculin? This again depends upon the judgment of the physician administering

[18] Lancet, October 31, 1908.

the treatment. Some desire to obtain as far as possible an absolute immunization; others are satisfied with procuring a tuberculin tolerance. Personally, I aim only to effect the latter state. When all symptoms have passed; when only slight coughing remains; when the patient ceases expectorating; when the weight has been fully or almost fully restored; when the patient is able again to resume light duties without in any way feeling the effort of exertion, I stop tuberculin therapy, even though a few physical signs of tuberculosis may still be present in the lungs. In other words, when the disease from clinical appearance and signs may be confidently diagnosticated as arrested, tuberculin injection should cease or, at most, be given at very long intervals.

I can best illustrate this by a case referred to me by Doctor Ethan Smith: This patient, aged twenty-three years, was kept on tuberculin for seven months; his condition at the beginning was most alarming; he had cough, high temperature, hemoptyses, numerous tubercle bacilli in the sputum, and he was considerably emaciated. He was kept in bed for three months, tuberculin therapy being given during this time, but not until the cessation of the hemoptyses and temperature. At no time after tuberculin injections were begun did he have any fever or any signs of a reaction. He steadily gained strength and weight until he was even heavier than before he took ill. He received his last injection of 1 c.c. of a 1 to 10 dilution of T. R. on March 6; at that time he weighed 141 pounds and was doing outdoor work. He still had a few tubercle bacilli in the sputum. I saw him again on March 21, when he was feeling well, had gained another pound, and had practically lost all physical signs. Upon this examination I could not detect any tubercle bacilli in the sputum. This patient has undoubtedly acquired a tuberculin tolerance, and the rest of his condition depends from now on upon the proper observance of hygienic laws.

The management of a case during injection is important. I have already referred to absolute rest in bed, preferably in the open air, for a long period of time, if fever is present or if the tuberculous focus is rapidly progressing. During this period the nurse or attendant, under the doctor's supervision, should keep careful records, especially of the temperature and weight. If the patient is ambulant, he should be taught to take his own temperature and to keep a record of the time and the amount of food he eats, his bowel movements, and any symptoms he may have. To treat tuberculosis properly, either with tuberculin or without it, requires a perfect understanding between patient and physician and a rational coöperation. The doctor must guide and instruct—the patient must be adaptable and observant. When my patients are ambulant, I especially instruct them about exertion. If possible, they must give up any active employment, although this is not always insisted upon. They are instructed to lie down from two to three hours after the injection.

Exercise is allowed in small doses at first and gradually increased. The beginning of a course of specific therapy often tries the patience of both physician and patient. At first no improvement is noticed; sometimes even a setback occurs. We must remember that this is a slowly progressing treatment extending over months, and we must constantly keep this fact before the patient. Often only after three months does the patient gain a little weight and a little hope and give the physician a little encouragement. In cases complicated with tubercular laryngitis the first encouragement is observed in the larynx. I have such a case now under treatment referred to me by Dr. A. S. Adler. The patient has an extensive lesion in the upper lobe of the right lung and a tuberculous laryngitis. The only improvement to date after six weeks of treatment is in the larynx. Dr. Robert Cohn, who is observing the larynx at intervals of two weeks, reports a very distinct change for the better.

Upon what class of cases should tuberculin be used? Here again opinions seem to vary. Lawrason Brown[19] in a recent article states: "The theory of the action of tuberculin plays an important role in the selection of patients. If it requires an active response on the part of the organism to produce a beneficial effect, it is useless to give it to patients who have lost all power of resistance and who fail to respond to stimulation." Therefore, it becomes apparent that the cases most desirable for tuberculin treatment are the incipient. Fever cases are undesirable, although Denys does not agree to this. Rapidly progressing cases should also never be given tuberculin. It may, however, be used with some degree of success in second and third stages. Pottenger's[20] statistics show that 65 to 90 per cent. of first stage cases get well, 30 to 65 per cent. of second stage cases, and only 5 to 10 per cent. of those in the third stage. Schrader, in his statistics, excludes only fever cases, and claims favorable results. Ritter[21] used tuberculin in 554 cases in his sanatorium, and comes to the conclusion that it has a favorable effect upon the disease. M. John states that in 200 cases treated with tuberculin the results are conflicting, proving negative in some of the apparently promising cases, while they were surprisingly good in others, even in some advanced cases.

During the last year reports have come of the use of tuberculin in surgical and genito-urinary tuberculosis, with favorable results. Edward Ochsner,[22] at the Washington Congress, reported that his cases of hip-joint disease were much influenced by the use of tuberculin and the final result hastened by it. P. Glässner[23] reports successful results in treating joint and bone tuberculosis with Marmorek's serum, and M. Strauss used Marmorek's serum in

[19] Boston Med. and Surg. Jour., 1908, clix, No. 4.
[20] Lancet Clinic, 1908, No. 7.
[21] Deut. med. Woch., xxxiv, No. 29.
[22] Jour. Amer. Med. Assoc., xli, Nos. 21, 19, 17, 16, 15.
[23] Deut. med. Woch., 1908, No. 29.

37 cases of various tuberculous processes in the bones, glands and bladder with gratifying results. N. Elsaesser[24] uses in surgical tuberculosis a combination of T. R. with Marmorek's serum. J. W. Walker[25] uses T. R. in tuberculosis of the genito-urinary organs. As already mentioned above, N. Raw uses Koch's T. R. with great success in all cases of surgical or bone tuberculosis. C. Kraemer[26] recommends tuberculin in the postoperative treatment of surgical tuberculosis, since he argues that the operation may cure the apparent lesion, but that the primary focus may still remain. This latter point has been proved in many cases by a positive tuberculin reaction, even after a total excision or extirpation of tuberculous glands.

Let us now pause and in conclusion consider carefully what constitutes the present-day status or conception of tuberculin as applied in the specific treatment of pulmonary tuberculosis and during the last year in nearly all forms of the disease. Is it a specific? I am compelled to reply in the negative. In the final analysis we can only regard tuberculin as a valuable adjunct to the hygienic and dietetic therapy of the disease. J. H. Pryor,[27] of Buffalo, most tersely states that a tuberculous patient "must have 18 square meals of oxygen per minute accompanied by three square meals of food per day." Trudeau,[28] who has used tuberculin over a longer period of time in more cases and more conservatively than any other man in the United States, shows that 18 per cent. more of treated incipient cases are living than of untreated, while 25 per cent. more of advanced cases who received tuberculin are living than of those who did not. He also says: "Many years ago, in spite of general denunciation of tuberculin and long before I knew anything about the statistical evidence, I had formed the opinion that tuberculin when administered had within certain limits a favorable influence on the course of the disease, and that the results of sanitarium treatment could be improved and made more permanent in many cases by its application. As years have passed I have seen no reason to change this opinion." Thus speaks one of our greatest authorities on this subject. We, with small experience compared with his, can only follow his lead. Tuberculin unquestionably is a valuable remedy in its present form and with the present improved method of administration, and is it not reasonable to hope that as the discarded tuberculin of 1890 was changed through the years into the valuable remedy of today, so may this remedial adjunct of today become a true specific in the future?

[24] Deut. med. Woch., 1908, No. 50.
[25] Practitioner, London, July 1908.
[26] Med. Klinik, iv, No. 4.
[27] Med. Record, January 4, 1908.
[28] M. Strauss, Marmorek's Serum in Surgical Tuberculosis.

ADAMS-STOKES DISEASE WITH COMPLETE HEART BLOCK, SHOWING A CONSPICUOUS LESION IN THE PATH OF THE AURICULOVENTRICULAR BUNDLE.

By Louis Faugeres Bishop, A.M., M.D.,
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The strong bearing of Adams-Stokes disease upon the myogenic doctrine that has been so fruitful in advancing precise knowledge of heart disease, is a good enough reason for recording the most typical and classical case that I have ever encountered in experience or literature.

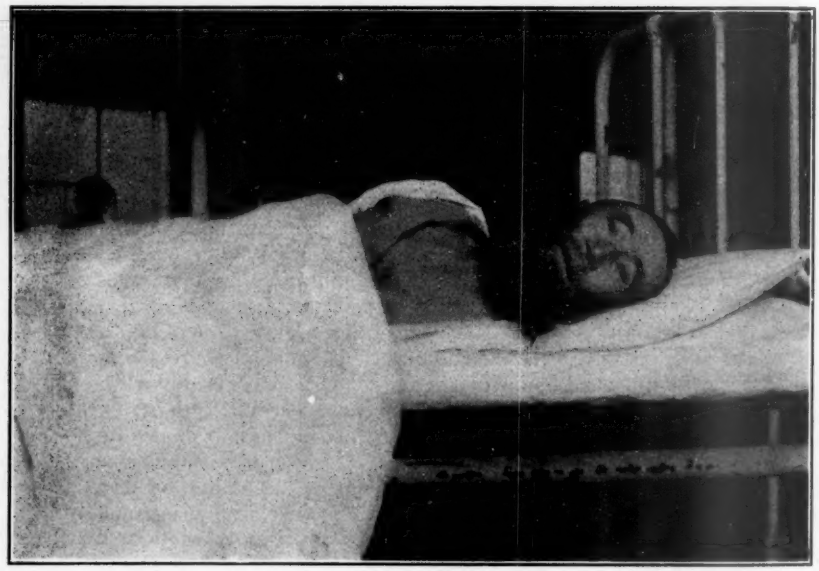

Fig. 1.—Adams-Stokes disease, showing the patient just recovering from a syncopal attack, with rapid pulsation visible in the depression above the clavicle.

The patient, Thomas M., a watchman, aged seventy-five years, was admitted to the Lincoln Hospital, on October 13, 1908, and died October 22, 1908. His family history was negative. He had previously had no important illness, except measles, whooping cough, and smallpox when a child. Later, he had muscular rheumatism, and twenty-five years ago had a sun-stroke, but had always

been considered a healthy, strong, hardworking Irishman. He drank whiskey moderately. Syphilitic history was denied.

On October 12, while in bed, he felt as though he was whirled around, and had a great buzzing in his ears, especially in his right one, in which he had been growing gradually deaf. After that he had three similar attacks, and came to the hospital complaining chiefly of these attacks and feeling weak. He said that the attacks and vertigo came on without premonition, and that between the attacks he felt perfectly well excepting that he was weak.

On admission, a physical examination, made by the house physician, Dr. Benjamin W. Seaman, and subsequently reviewed by me, showed a patient fairly well developed but poorly nourished, sitting up in bed with an alert and intelligent expression. He was able to answer questions perfectly, and gave a clear account of his symptoms. An examination of the chest showed the heart apex in the fifth space, three and a half inches from the median line. The heart was regular in action, except for occasional differences in the interval between beats, and there were no murmurs. Above the right clavicle venous

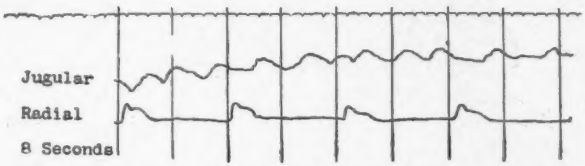

FIG. 2.—Tracing of the jugular and radial pulses during eight seconds.

pulsations were visible, two or three times more frequent than the apex beat. The patient's eyes reacted to light and accommodation. The tongue was protruded straight, and was deeply coated. The liver was not made out enlarged. The extremities were negative except that the knee-jerk was not obtained. No further physical signs of disease were obtained. The radial artery was not thickened, even to the degree that would be expected in a patient of this age.

The urine examinations revealed a specific gravity of 1020 to 1024, no albumin, no sugar; urea, 1.8 per cent. (9.1 grams in the twenty-four hours).

The diagnosis of Adams-Stokes disease was unhesitatingly made by all those who observed the patient. During his stay in the hospital, he was treated with potassium iodide, but his syncopal attacks recurred daily, and sometimes several times during the day. The iodide caused symptoms of iodism, and was discontinued. This patient was under observation for nine days, and at the end of that time he became delirious, and one morning his pulse dropped to 20, his respirations rose to 28, his temperature fell to 96°, and he died suddenly.

The pulse-respiration ratio, recorded while under observation, at intervals of four to eight hours, was as follows: 38 to 20, 40 to 22, 36 to 24, 36 to 24, 32 to 20, 30 to 22, 32 to 20, 34 to 24, 32 to 20, 36 to 22, 34 to 28, 30 to 20, 34 to 18, 30 to 20, 32 to 18, 34 to 28, 32 to 22, 30 to 20, 30 to 20, 28 to 20, 30 to 20, 30 to 20, 32 to 24, 32 to 24, 28 to 20, 34 to 24, 32 to 24, 36 to 24, 30 to 20, 32 to 24, 32 to 24, 28 to 29, 26 to 24, 30 to 24, 32 to 20, 28 to 24, 28 to 24, 28 to 24, 28 to 24, 26 to 20, 30 to 24, 26 to 20, 28 to 26, 24 to 28, 20 to 28.

FIG. 3.—Heart showing a calcareous nodule in the region of the bundle of His.

The photograph of the patient (Fig. 1) shows him just recovering from a syncopal attack. In the depression visible above the clavicle the comparatively rapid jugular pulsations could be seen. The

tracing (Fig. 2) shows the radial and jugular pulse during eight seconds.

The postmortem examination was made by Dr. J. H. Larkin. The heart (Fig. 3) showed a calcareous nodule, situated precisely in the path of the bundle of His. This nodule was evidently the cause of the complete heart block observed during life.

THE TECHNIQUE OF OPERATIONS ON THE LOWER PORTION OF THE URETER.[1]

By Charles L. Gibson, M.D.,

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In performing any operation, but more particularly in the abdomen, a sufficient exposure of the operative field is necessary for efficient and safe work. There are few parts of the body where it is so difficult to obtain these conditions as in operations at the pelvic outlet, particularly when seeking to remove stones situated in that portion of the ureter which lies below the pelvic brim. Of course, it is easy enough to make a ruthless incision which resembles the technique of the morgue rather than the operating room; but in this country, certainly, we very justly do not consider that the mere completion of an operation spells success: we judge its value by the end results. For it cannot be said to be a gain for a patient to have the trouble caused by the presence of a ureteral stone replaced by a huge and weak scar which allows of eventration of the abdominal contents, a condition of permanent danger and discomfort.

In work which entails opening the ureter, I assume that the weight of evidence is in favor of procedures which do not permit urine to find its way into the peritoneum. Other debatable points are: Shall we attempt to close an intentionally opened ureter, and, shall we provide prophylactic drainage against a possible urinary leak—in other words, shall we deliberately relinquish the opportunity to secure complete closure and union of this abdominal wound?

In my judgment the ideal method of performing operations on the lower ureter should fulfil the following conditions: The incision of the abdominal wall should be of such a size and situation as to give an ample exposure for the easy recognition of the ureter, the necessary manipulations, and security from injury to the other pelvic structures, particularly the iliac vessels. The incision should be extraperitoneal. It should be possible to make

[1] Read at a meeting of the American Association of Genito-urinary Surgeons, June 1, 1909.

the ureter so freely accessible that any incision in it can be as easily and accurately repaired as a lesion of the intestine. There should be no unnecessary trauma or malhandling of the tissues, so that the completion of the operation should leave a perfectly dry field, doing away (when the continuity of the ureter has been restored) with the necessity of drainage—a prophylactic measure against subsequent hernia. The incision of the abdominal wall should be so planned as to produce the least damage, allowing when it is closed without drainage a firm union without risk of hernia. Finally, the whole operation should be so simple, so free from annoying hemorrhage or other pitfalls, that it can be performed without undue waste of time—half an hour or less.

These ideals, I believe, can be realized by a suitable exposure of the ureter and the lower pelvis by an incision which I offer for consideration.

The description of the incision and the various steps are as follows: The original idea of the incision was to utilize the advantages of the Stimson-Pfannenstiel incision, which is used frequently, particularly in gynecological laparotomies. I have used it in probably a hundred such laparotomies, and believe it is the least likely to be followed by hernia. Familiarity with the anatomy of the abdominal wall and abdominal incisions generally will be necessary for a successful execution of the several steps.

The skin incision runs from the mid-line about a finger's breadth above the pubes, horizontally outward nearly parallel to Poupart's ligament at first (Fig. 1), and curves rather sharply upward at its mid-point to end about opposite the anterior superior spine of the ilium. This incision is deepened in the same line through the aponeurosis of the external oblique and the internal oblique muscle, —the latter is the only structure which suffers any real damage, and only to a slight degree, for the lower part of the incision runs about parallel to its fibers, only the ascending leg cuts across a small part of these fibers. The incision stops short of the transversalis, which is not disturbed at all. With efficient retraction of the upper flap the external border of the rectus muscle is identified (Fig. 2) and the *fascia* of the transversalis is now divided by a vertical incision close to and parallel to the rectus—that is, at *right angles* to the original incision. Two retractors are now inserted, the outer one retracts the cut edge of the transversalis outward, the other (Fig. 3) pulls the rectus muscle well toward the mid-line. A generous space is thus obtained, situated well toward the mid-line (the lower part of the ureter is practically in the mid-line, and difficult of access by other extraperitoneal exposures). The floor of this space is occupied by the peritoneum. The patient being in a complete Trendelenburg position, the peritoneum is easily and gently pushed away, and a free access to the pelvis is secured. So ample is the space and view, that the whole hand can be introduced under the control of

the eye. The ureter is released from its surroundings and easily brought to the external level of the wound (Fig. 4). In this way it can be handled as readily and freely as a loop of intestine.

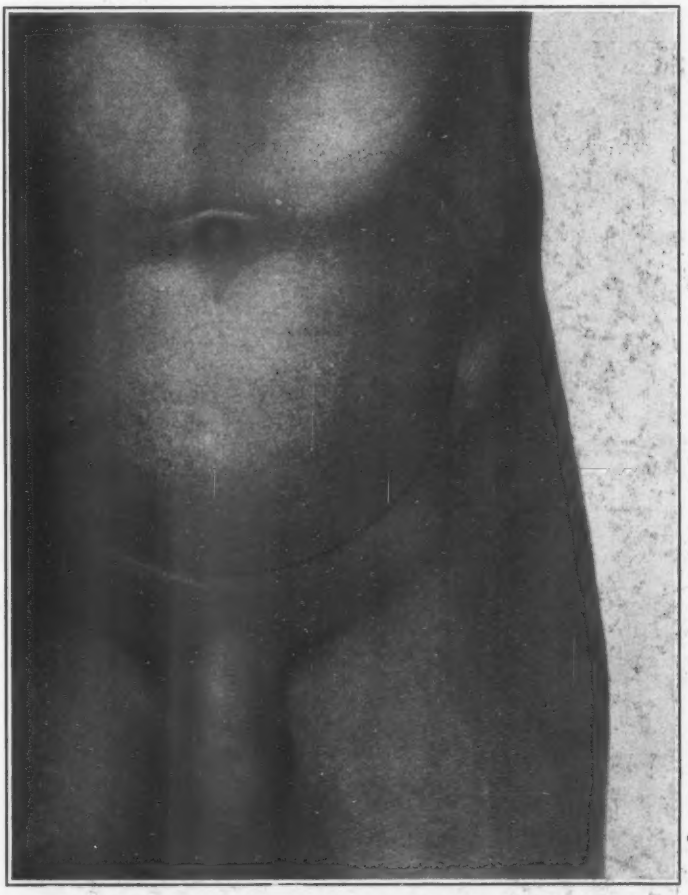

FIG. 1.—The superficial incision.

After removal of the stone, the ureter is closed with a double layer of the finest chromicized catgut, the first going through all the layers, the superficial sutures reinforcing the first. The ureter is then dropped back. The operative field, protected by a gauze pad during the ureteral manipulations, will be found perfectly dry. The wound is closed without drainage. The transversalis fascia is

sutured separately with catgut. Continuous sutures of medium-sized catgut (preferably moderately chromicized) are used for the combined internal and external oblique layer. A few interrupted fine catgut sutures are used for the superficial fatty layer. Very

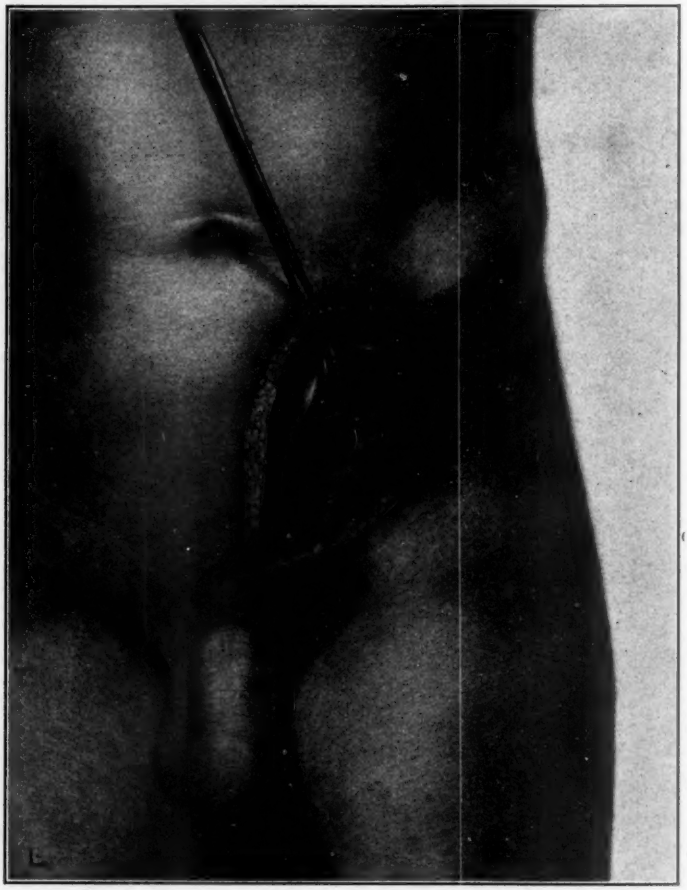

FIG. 2.—The upper flap consisting of skin, external and internal oblique muscles is retracted. The dotted line represents the line of incision in the transversalis fascia.

fine continuous silk sutures are used for the skin. A sterile dressing and a firm binder are applied. Rest in bed for ten days is enjoined. when, if asepsis has been irreproachable, the wound will be found firmly healed, and the patient may resume his usual activities.

That these ideals can be realized is demonstrated by a brief recital of the following cases:

CASE I.—W. W., aged sixty-two years, male, was admitted to St. Luke's Hospital, November 13, 1907. For the past two years he

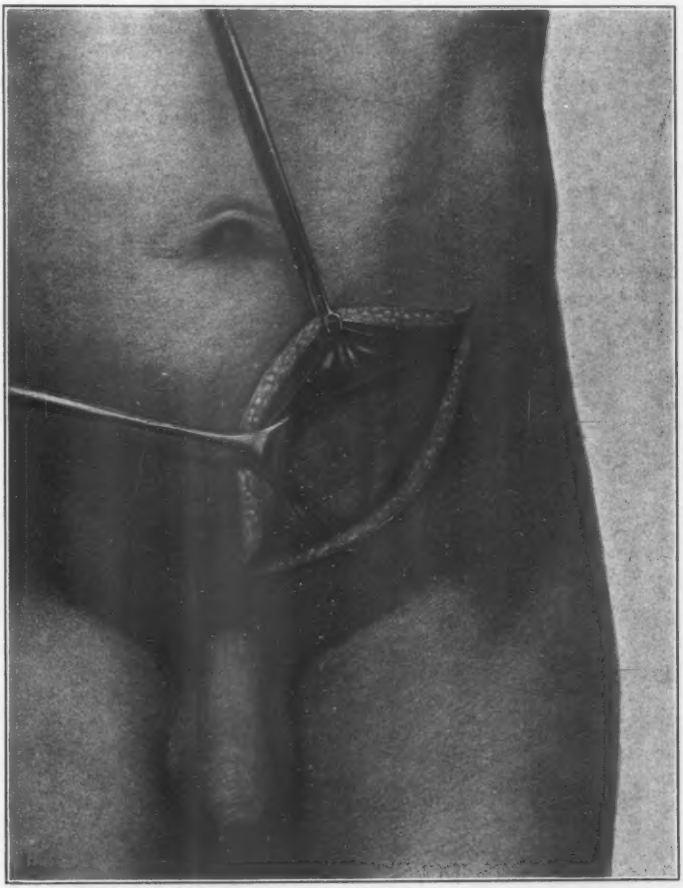

FIG. 3.—The edge of the rectus muscle is strongly retracted inward; between it and the cut edge of the transversalis fascia the peritoneum is exposed.

has had a dull pain over the sacral region. The urine is cloudy and sometimes bloody. An *x*-ray examination showed the presence of a large stone (Fig. 5) in the lower left ureter. Operation, November 14, 1907. Under ether anesthesia the stone was easily

palpated per rectum. It was removed according to the technique just described. Time of the operation, thirty-five minutes. Convalescence was uneventful. The highest temperature (rectal) was 100.4°. The wound healed by first intention. On November 29 the patient

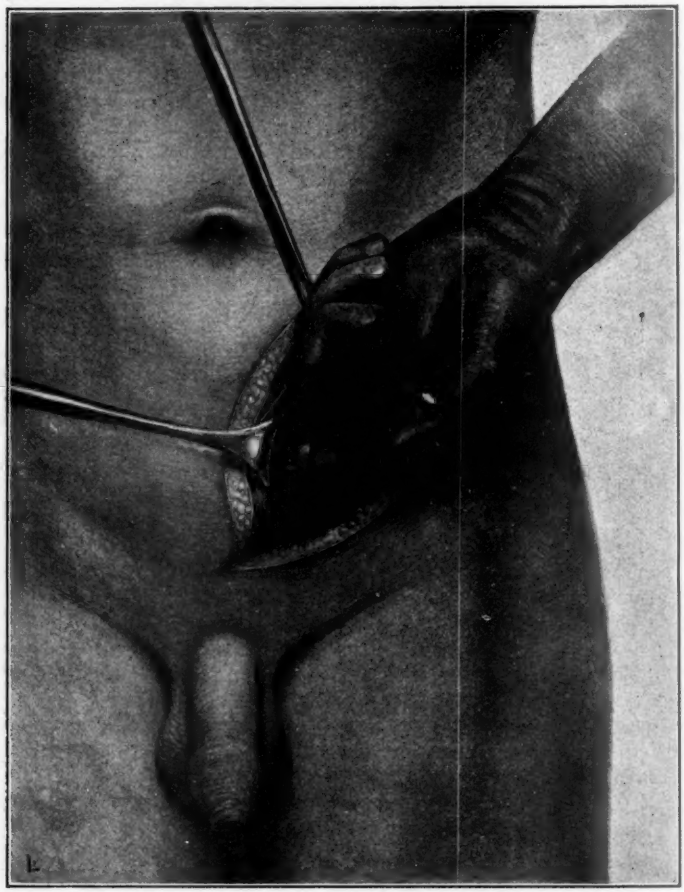

FIG. 4.—The peritoneum has been pushed upward. The ureter is lifted out of the pelvis and brought to the level of the external wound.

was allowed up. On December 3 he was discharged cured. At an examination on May 26, 1909, the scar (Fig. 6) was firm, and there was no hernia.

CASE II.—P. M., male, aged thirty-eight years, was admitted to St. Luke's Hospital, March 11, 1908, having been previously in the hospital for the same trouble. The hospital *x*-ray technique having failed to find a stone, although the symptoms were classical,

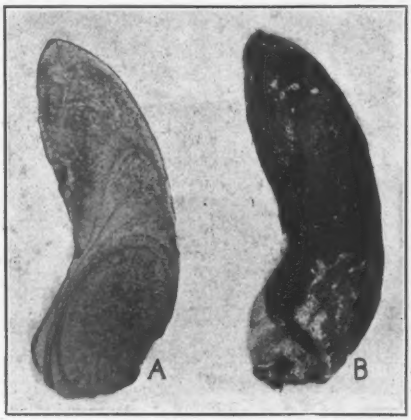

FIG. 5.—Ureteral calculus from Case I. Weight, 18 grams. *A*, sawn surface; *B*, external surface.

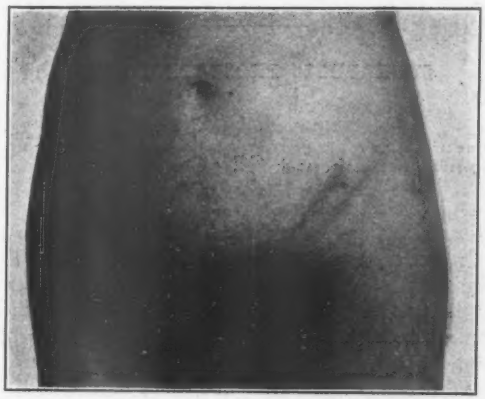

FIG. 6.—Scar eighteen months after the operation (Case I).

I invoked the kind assistance of Dr. W. E. Cauldwell, who promptly located the stone in the lower part of the left ureter. Operation was done on March 17, 1909, by the technique described above; the time of operation was twenty-eight minutes. Convalescence

was uneventful. The highest temperature (rectal) 101.4° occurred the day after operation. At the first dressing, on March 24, the wound was well healed. On March 27, the patient was allowed

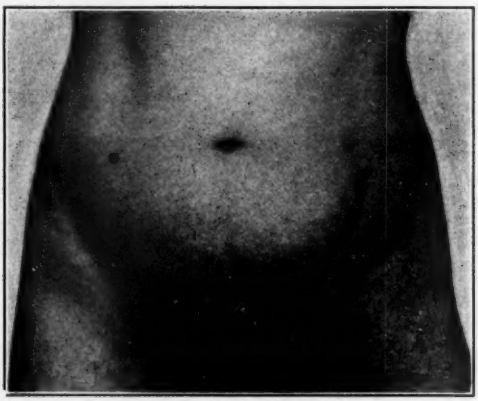

FIG. 7.—Scar fourteen months after operation, (Case II.)

up. On March 30, feeling very well, he was allowed to go home, being discharged cured. An examination on May 27, 1909, showed the scar (Fig. 7) firm, and no hernia.

SUPRAPUBIC PROSTATECTOMIES.

BY CHARLES H. CHETWOOD, M.D.,

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IF I read aright the temper of the surgical mind today, we no longer speak of different camps in prostatic surgery—the perineal prostatectomist and the suprapubic prostatectomist. An understanding has developed between these disputing factions, and it is more generally recognized that, as there are different kinds of prostatic enlargements—broadly speaking, those that are high up and those that are low down—so there are some cases best suited to the high or suprapubic operation and others to the low or perineal; while there are borderland cases which are as well attacked by either one of these routes.

The statistics prepared by Watson and Cunningham[1] seem to show a better percentage of complete recoveries following the

[1] Diseases and Surgery of the Genito-urinary System, 1909.

suprapubic operation as compared with the perineal route; while the percentage of operative risk favors the selection of the perineal operation. Yet a progressive decrease in mortality is apparent in both instances, and up to now the perineal technique has probably received much greater attention than the high operation. I am disposed to believe that the future will develop the latter operation to a considerable extent.

As it is true, as is clearly set forth by Waston, that the suprapubic is a complete operation, having a large percentage of cures and a small percentage of operative complications, and is rapid of performance, under conditions which afford free access to the gland, it is a matter of serious importance that effort should be made to improve the technique and bring down the mortality rate.

This communication is devoted to the consideration of six cases of suprapubic prostatectomy, representative of different phases of the subject, operated upon in the last six months, except one of them, which was operated upon somewhat more than one year ago.

A brief resume of the cases is as follows: The patients are aged seventy, seventy-two, sixty, seventy-five and sixty years respectively. The duration of symptoms was from one to twenty years. Urination: Complete retention in three cases; frequent and difficult urination in the remainder, with residual urine from four to twelve ounces. Pain was present in a greater or lesser degree in all cases. Infection had occurred in all of them with one exception; that is to say, the urine was cloudy and bacterial, and in three there was ammoniacal decomposition. The urethral length varied from eight and one-half to nine and three-quarter inches. Rectal examination revealed the prostates to vary in size from that of a slight median enlargement to five times the normal dimensions. Bladder exploration was possible in all but one case; and it was possible to recognize with the sound an intravesical median projection. Examination of the urine showed moderate implication of the kidneys in half the cases. Other complications were a stone in one case, glycosuria in one case, carcinoma in one case, and one patient suffered from extreme obesity.

Operation was primary in all cases with one exception, in which it was performed secondarily to a previous perineal prostatectomy. The operation was done in two steps in one case, on account of the unsatisfactory general condition, very foul urine, and much prostatic congestion. Convalescence was prompt and uninterrupted in all except one case, in which it was protracted.

The latest report following operation varies from one to thirteen months. The result has been return of voluntary urination in all cases; and elongation of interval between the urination from complete retention and fifteen minutes to one hour frequency before, to a minumim of two hours and a maximum of six hours following operation. The urine has become clear in three cases, and remains

cloudy, but not decomposed in three. A swollen testicle occurred in three cases following the operation; in all of these cases there was a history of previous trouble in the testicle. In one case active epididymitis occurred before the operation; a double vasectomy was performed, and no relapse occurred after the prostatectomy. In the other cases there had been no previous trouble with the testicles, and none occurred after prostatectomy.

The operative technique followed is practically the same in all cases. Special attention is given to certain details to facilitate the operation, shorten its duration, and enable the hastening of post-operative convalescence. Of the last consideration, the most important is that of bladder drainage.

The patient is brought to the operating room with the bladder washed. The anesthetic used has been in most instances ethyl chloride and the drop ether method. The bladder is emptied, and while the catheter is left in place the patient is immediately put into the Trendelenburg position. An incision is made above the pubis, about three inches in length, separating the muscles and exposing the pre-vesical fat. An assistant now inflates the bladder with air, while the wound is separated by retractors. The structures overlying the bladder are stripped upward to the upper extremity of the wound with a piece of gauze. Incision is now made through the bladder, running well downward. This incision may be enlarged later, after the exploration with the finger has been completed.

Exploration with the finger is usually sufficient to give an adequate idea of the prostatic growth, but retractors may be inserted and ocular observation made if desired. In one of the cases of this series the cancerous nature of the prostatic growth was recognized by palpation at the time of operation. A place is selected for the incision of the mucosa over the prostatic growth, which is usually to one side of the median line at a point where the lateral and median growths meet. Into this incision the bare finger is inserted, and by gentle manipulation it is ascertained that a good line of cleavage is obtained. Separation of the prostatic growth is then accomplished with the aid of the gloved finger of the other hand in the rectum.

As to the all-important matter of drainage, I have for two years past been using a double tube, one large and one small, for continuous irrigation; this in the first twenty-four to forty-eight hours is an important feature, to prevent blood-clotting inside the bladder. When in Europe last year I found that in Paris the surgeons were using a similar double current tube, designed by Dr. Marion, which did not differ in principle from those that I had been using for some time previously. This resembles the Freyer tube in its unusually large size, with the addition of a small catheter-like tube for irrigation (Fig. 1). The extra large size is intended to permit free evacuation and prevent retention of clots. Freyer

uses an extraordinarily large tube without any irrigating attachment. I have found of late that drainage is just as good with the irrigating attachment when a smaller tube is used, allowing the insertion of two or three stitches to close up the bladder wound so that shortening of the convalescent period is the result.

The size of the tube used is from three-eighths to five-eighths of an inch in diameter, with the small catheter attached; besides this, however, I often use an indwelling catheter in the urethra, both because it is useful to irrigate through, should the other attachment become clogged, and because it smooths the newly forming posterior urethra during cicatrization, and is already in place for use after the bladder tube is removed, thus avoiding the unnecessary bruising of the tissues which sometimes occurs upon the first introduction of a catheter after operation.

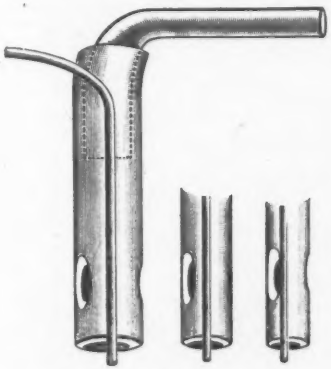

FIG. 1.—Suprapubic drainage tubes with irrigating attachments.

The prime object of good drainage is to keep the bladder clot-free and the patient comfortable during the first few days. I find that the method described adequately fulfils these conditions. It is at the period when the suprapubic tube becomes somewhat loose that we have experienced difficulty in keeping the urine from overflowing alongside. Various systems of siphonage have been resorted to, but have not proved successful. I have employed a system of siphonage designed many years ago, and have had constructed an apparatus on the same principle as that of Dr. L. W. Bremerman, of Chicago, which is not continually getting out of order, and keeps the patient dry. This (Fig. 2) consists of an irrigator jar which empties at slow speed into a tip cup; this overflows at regulated intervals into a funnel, and thus provides intermittent siphonage of the bladder. This siphonage is especially useful during the first five to seven days after operation, when it is important to keep the suprapubic

wound clean and as dry as possible, so as to promote union of the parts sutured.

The period when it is most difficult to keep the patient dry and comfortable is that between the time when the suprapubic tube is taken out and before the suprapubic fistula is sufficiently healed to permit voluntary urination. During this period I utilize the

FIG. 2.—Apparatus for automatic siphonage of the bladder.

indwelling catheter in the urethra, strapping the suprapubic wound over tightly with adhesive straps. This stage is reached in a much shorter period when the drainage opening left at the time of operation is comparatively small, the tissues not lacerated, and early granulation encouraged by keeping the wound comparatively clean and dry by means of satisfactory drainage provision. The catheter is kept in place from four to five days to a week, and then voluntary urination occurs with moderate leakage.

In one of the cases of the series reported, a fistula remained for a number of months, but this was on account of deterioration in general health and the great obesity of the patient. Ultimately satisfactory closure occurred.

The cases, briefly, are as follows:

CASE I.—April 1, 1908. Aged seventy years; duration twenty years. There was complete retention. The prostate was very large, and much congested. The urine was excessively purulent and foul. Both rectal touch and bladder exploration recognized a good-sized median intravesical projection. The general condition was much depreciated, on account of extreme obesity, diabetes, and general toxemic debility.

FIG. 3.—Case I. Bilateral and median prostatic hypertrophy and vesical calculi.

The operation was done in two steps: a primary suprapubic drainage, at which time two calculi were removed; and ten days later complete prostatectomy (Fig. 3). At this time the patient's general condition showed marked improvement, and as a result the removal of an extensive growth caused the patient little or no surgical shock.

The postoperative convalescence was long, on account of slow healing of the wound, due to great obesity. A fistula persisted for several months, but eventually healed entirely. An intercurrent epididymitis occurred and suppurated.

At present the patient urinates every four to six hours, the bladder empties, the general health is excellent, and sugar has entirely disappeared from the urine.

Remarks. This case is an example of advanced prostatic hypertrophy producing complete retention; and a bad general condition due to toxemia, great obesity, and glycosuria. It illustrates the conservative effect upon both general and local conditions of a preliminary drainage as a preparatory measure.

CASE II.—November 29, 1908. Aged seventy-two years. This patient has been getting up at night to urinate once or more often for a year, and in the past six months the frequency has become much increased; at times urination has been as frequent as every quarter to one hour, and at night six times. No instrument was

FIG. 4.—Case II. Symmetrical prostatic hypertrophy, showing carcinomatous foci.

passed until three weeks ago, when eight ounces of residuum was obtained. He never passed blood spontaneously. The urine was clear and sparkling. The prostate per rectum was as large as a golf ball, and of unusual hardness. The patient had lost six pounds in weight.

On December 1, 1908, suprapubic prostatectomy was performed. The prostate was enucleated with difficulty from a rather thickened capsule, a piece of which was also removed for laboratory examination (Fig. 4). The patient made a good recovery, left the hospital, and returned to his home in South Carolina, about three weeks after the operation. The laboratory reports showed carcinomatous foci throughout the gland; but the capsule proved to be simple inflammation, and contained no signs of neoplasm. The patient reports excellent health in December, 1909 (one year after operation); his condition has remained satisfactory so far as his own or his attendant doctor's observation is able to determine.

Remarks. The suprapubic operation in this case permitted thorough inspection of the vesical cavity and complete removal

of the gland, without disturbing the bladder function. Whether a more extensive operation would afford a greater immunity from recurrence is a question.

CASE III.—Aged sixty years. The patient's history dates back four years, when he commenced having frequency and urgency of urination, following an exposure and cold, when he had his first attack of complete retention. The frequency and urgency of urination gradually became worse until the demand was almost constant. Two years ago this condition reached its most acute stage, when the patient was able to urinate but a teaspoonful at a time, and compelled to sit down to accomplish this. At this time he entered one of the large city hospitals for relief, and a transcript of the history shows that he was operated upon in April, 1907. A description of the operation states that through a V-shaped incision the bulbo-urethra was reached; an opening was made into the median portion upon a staff, the capsule of the prostate exposed, and a prostatic retractor introduced through the opening in the membranous urethra; through incisions made in the capsules on both sides of the prostate, one-half inch from the median line, the prostate was removed in three pieces.

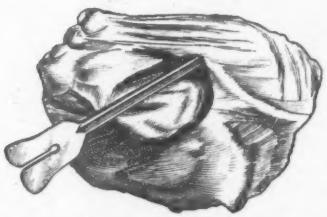

FIG. 5.—Case III. Large median lobe left by a previous perineal prostatectomy.

In April, 1909, he appeared at the Polyclinic Hospital with almost complete retention of urine, great difficulty of urination, and it was not possible to introduce a Nélaton or woven silk catheter. A metallic catheter was introduced with some difficulty. The finger introduced into the rectum felt, with the sound on the floor of the bladder, what seemed to be a prostatic growth of a size much beyond the normal. The urethral length was nine inches.

In the early part of March, 1909, the patient was subjected to suprapubic prostatectomy and a large symmetrical growth was removed, including the posterior section of the prostatic urethra (Fig. 5). The patient made a good recovery. The wound healed readily, and voluntary urination returned. A certain amount of dribbling, however, has persisted between the urinary acts.

Remarks. This case illustrates the ineffectual results of an attempt at complete removal of the prostate by a deliberate and, from the description, carefully performed perineal operation. On

account of a remaining middle lobe, of large size, producing complete retention, a secondary operation was necessary; the large intravesical projection was readily removed by a suprapubic operation, which was evidently not found accessible at the perineal operation.

Case IV.—October 4, 1908. Aged sixty years. The patient complained of complete retention of a few days' duration, following upon more or less acute irritability of the bladder for several weeks back, when he thought he contracted an acute gonorrhea; before this there was nocturnal frequency. He had had gonorrhœa two years before, but no previous retention. The prostate per rectum was two and one-half inches in diameter, generally symmetrically enlarged.

Fig. 6.—Case IV. General prostatic hypertrophy with a median projection.

The prostate (Fig. 6) was removed by enucleation in one piece through an incision in the vesical mucosa. The patient was up in the ward in two weeks, and made an excellent recovery without postoperative complications, the bladder emptying completely, and the urine coming clear.

Remarks. This was a borderline case, that might have been done as well by either perineal or suprapubic route. The result could hardly be improved upon.

Case V.—February, 1909. Aged seventy-five years. Complete retention the day previous to admission. Symptoms of prostatitis of seven years' duration. There had been two previous attacks of retention, two and seven years ago. The prostate per rectum was four inches in diameter, and felt globular and firm; it extended upward centrally.

The urethral length was ten inches. Exploration with a sound detected a median obstruction.

Complete removal of prostate was effected suprapubically without difficulty (Fig. 7). Continuous drainage was provided in the usual way. Suprapubic drainage was used for ten days, following which a change was made to an indwelling catheter, which was retained for about two weeks; during this time the suprapubic sinus

healed, and voluntary urination and complete emptying of the bladder were satisfactorily accomplished.

FIG. 7.—Case V. Middle lobe of the prostate causing complete occlusion of the urethral orifice.

CASE VI.—Aged sixty years. This patient's symptoms had existed for one and a half years, during which period he had had increasing difficulty in passing water, and greater urgency and nocturnal urination. On November 30, 1908, he had almost complete retention of urine, being able to pass but one or two ounces without the use of a catheter, and in the spring of 1909 he became practically entirely dependent upon the use of a catheter. The urine was cloudy, but not decomposed. The urethral length was nine and one-half inches. Rectal examination showed a symmetrically enlarged prostate, extending backward beyond reach. The bladder exploration revealed resistance upon the floor, as of a middle

FIG. 8.—Case VI. A median lobe of the prostate with two bilateral projections.

lobe. The kidneys were not affected. The patient had constantly recurring swollen testicle, and on this account was primarily subjected to a double vasectomy, which afforded complete relief.

On April 30, 1909, suprapubic prostatectomy was done, the prostate being removed in three portions (Fig. 8). The middle lobe, which showed a symmetrical enlargement, imposed upon the urethral orifice and two other symmetrical bodies from the lateral region. The patient had no untoward symptoms. He was sitting up out of bed in a week. In about ten days the drainage tubes were removed and the indwelling catheter effectually drained the bladder, there being only slight moisture at the site of the suprapubic wound. At the end of the second week the catheter was removed and the

patient was able to urinate voluntarily, emptying the bladder, and the wound sinus was practically closed.

Remarks. Cases V and VI illustrate simple, straightforward suprapubic prostatectomies, presenting ideal results and the accomplishment of satisfactory drainage by means of irrigation and siphonage with a moderate sized tube; this permitted suture of the bladder walls around a small drainage opening, which, combined with the use of a retained catheter, was the means of affording a short and comfortable convalescence and early return to voluntary urination.

THE PRINCIPLES AND TECHNIQUE OF THE WASSERMAN AND NOGUCHI REACTIONS, AND THEIR COMPARATIVE VALUE TO THE CLINICIAN.

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Introduction. A syphilitic taint in an individual is of importance not only to the diagnostician and therapeutist, but also to the social economist. A means for its detection becomes a valuable contribution to our diagnostic methods, the more so the greater the sensitiveness of the reaction as established by its coincidence with clinical findings. The Wasserman reaction, based upon an ingenious principle, worked out by Bordet and Gengou, gives to the experienced laboratory worker a very satisfactory means of diagnosticating syphilitic affections, even in individuals who were infected years ago, of course excluding a dormant condition or patients at the end of a successful treatment. Having analyzed over 700 sera from dubious, negative, and distinctly luetic individuals, I venture to give my results with the Wasserman and Noguchi tests, considering as an introduction the various principles of immunity upon which the reaction of complement deviation depends.

Reaction of the Organism to Infection. When a child is affected with diphtheria, the poison produced by this bacterium produces most of the symptoms of the disease. When the patient survives, it is possible to demonstrate in his serum substances which are capable of neutralizing the toxin of the diphtheria bacillus. The antitoxin to this disease is extensively manufactured by drug concerns by infecting horses with diphtheria, and at a convenient time withdrawing from the jugular vein some serum which contains the antitoxin. We learn from this simple exposition that an organism infected with a certain disease, in order to protect itself, produces in its body a substance which neutralizes the bad effect of the invading factor. Not only does the animal body respond in such a specific manner against bacteria, but the same is evident when we

inject certain acellular vegetable poisons or cells from another animal.

It is by no means a difficult task to produce in the serum of a suitable animal substances which will destroy the red blood corpuscles from another animal. This is accomplished by injecting into the animal such cells as we wish to destroy. One may produce in the rabbit (the animal used for the production of antibody) substances which are capable of destroying sheep red cells, bovine red cells, or human red cells, the specific quality depending upon the cells used for immunization.

In order to be able to grasp the steps in the Wasserman reaction it is indispensable to be acquainted with the steps involved in demonstrating antibodies of any kind formed accidentally (by disease) or purposely (in immunizing) in the body fluids of an animal. Ehrlich showed long ago that in the demonstration of antibodies, or, as he called them, amboceptors, three distinctly different substances are required in order to form a complete reaction: first, the cell or poison against which we wish to immunize, or, more plainly, against which we desire to obtain an antibody; second, the antibody (or amboceptor) obtained by repeated injections of the special cell or poison into the rabbit (or any other suitable animal); third, a completing substance—the complement. This latter substance is present in variable quantities in the sera of all animals, its quantity being rather constant in guinea-pigs. It is destroyed by heating serum at 56° or 57° for one-half hour, and is similarly affected by various other physical agents. This is not the case with antibodies which are comparatively thermostable. We have, then, three factors: (1) A cell to be destroyed or a poison to be neutralized; (2) a substance capable of doing this—the amboceptor or antibody; and (3) a completing substance, without which the reaction cannot take place—the complement.

Ehrlich and others, in order to impress the reaction upon the minds of men interested in immune processes, made use of diagrams. To make it still more familiar, let a lock represent the cell, a key which fits it the antibody, and the hand that will turn the key the complement. By giving a lock to a smith we can get a key made to fit the specific lock exactly. When we inject cells we get an antibody which exactly fits the cell injected, and the same is true when we inject a bacillus or a poison. All these substances capable of producing antibodies (antibody generators) are known as antigens.

To determine whether a bacterium was killed or a poison neutralized by being exposed to the action of a specific amboceptor is not as simple a process as the demonstration of the destruction of red blood corpuscles by an amboceptor directed against them. A suspension of red blood corpuscles minus amboceptor and complement gives an opaque red mixture; when we add the amboceptor plus complement and incubate at 37°, the opacity disappears and a clear red

fluid results. It is apparent that hemolysis or destruction of red cells is a phenomenon that can readily be seen in vitro, and its presence signifies that the three substances spoken of above are present in the test-tube. If any one of the three is not there, or is present in an inactive state, the red cells will remain unaffected and the mixture will retain an opaque red color.

Hemolysis. The phenomenon known as hemolysis depends upon the destruction of red blood corpuscles. There are many reagents capable of doing this, such as distilled water, acids, and alkalies. It is also possible to form in warm-blooded animals substances which will bring about hemolysis against certain red blood cells. This is accomplished by injecting an animal (a rabbit or goat) with the cells of a sheep or any other animal. The serum from such a rabbit, when brought in contact with the cells of the sheep, will cause the mixture to become clear (hemolysis). The same amount of serum from an untreated rabbit will have no effect on a similar suspension of sheep cells. The substance produced in the rabbit's serum is known as the antisheep amboceptor, and together with sheep cells and complement (from a guinea-pig) is known as a hemolytic system.

The Bordet-Gengou Phenomenon. The principle applied in the Wasserman reaction depends upon a test originally devised by Bordet and Gengou in 1901. At that time these authors conceived the idea of demonstrating in vitro the presence of unknown amboceptors (or antibodies) by attempting to fit on to them the corresponding antigen. It is clear that in order to do this, complement is absolutely necessary. Supposing, then, the antibody at hand to be from a patient who suffered from typhoid, this antibody ought to anchor itself to the organism responsible for its specific production, the typhoid bacillus, or suitable extracts made from typhoid cultures. This actually takes place and, if complement is present, forms an undisruptible triad; in other words, typhoid antigen is bound to the available complement by the typhoid amboceptor. If we should introduce into the very same test-tube a mixture consisting of sheep cells and some antisheep amboceptor, no hemolysis will take place, for the simple reason that in order to do so complement is necessary, and, as said before, the available complement has been bound—or deviated—by the preëxisting well-fitting typhoid antigen and typhoid antibody. If the serum of the patient had not contained typhoid antibodies (in case of acute miliary tuberculosis), the complement would not have been bound to the typhoid antigen, but would have been left free, and a hemolytic system consisting of sheep cells and antisheep amboceptor would be completely laked—or dissolved—for the available complement was left free to act, was not deviated or bound up.

We learn from the above exposition that in order to prove the presence or absence of certain antibodies, we make use of the

phenomenon of bound or unbound complement, utilizing a hemolytic system simply as an indicator. Exactly the same principle is applied to the serum diagnosis of syphilis. Unable to produce a growth of Spirochæta pallida upon any culture medium, we have to be contented with organ extracts containing them in greatest numbers; for this purpose the liver of the luetic fœtus furnishes the requirements. The extract produced is known as luetic antigen, and need not confuse anybody, for we know that an antigen is a body capable of forming antibodies. If an individual has had syphilis some years ago, he would also have syphilitic antibodies in his serum which, when brought in contact with the extract from the syphilitic liver, would invariably, as pointed out before, bind complement, and a hemolytic system (sheep cells or any other red cells with the corresponding amboceptors) will never be affected on account of lack of complement.

I hope the very rudimentary style of offering to the reader an explanation of the phenomenon of complement deviation will be remembered on account of the simplicity of terms used and the simple analogy with more familiar subjects. I will now consider the actual steps of the reaction, giving it in detail and as plainly as the untrained worker desires it.

Technique of the Wasserman Reaction. *Principle Involved.* As mentioned before, antibodies will attract complement if the antigen responsible for their formation is present in the same test-tube. In the Wasserman reaction a serum containing antibodies capable of uniting with the antigen used (a substance containing lipoids), and thus deviate the introduced complement, will not permit hemolysis to occur if sheep cells and their antisheep amboceptor are subsequently placed in the same tube, and for obvious reasons—the complement was bound or deviated previously by conditions suitable for such an interaction. If the patient's serum does not contain the required antibody, the introduced complement will remain unbound and in a fit condition to destroy the sheep cells when subsequently introduced with their antisheep amboceptor.

Modus Operandi. (1) Obtaining blood from patient: A fairly stout piece of rubber tubing is placed a little above the elbow and held snugly in place by an artery clamp. Do not obliterate the pulse. This brings into prominence the veins at the bend of the elbow. To a stout hypodermic needle (I use a 19 bore—one and one-half inch needle) attach a two inch piece of rubber tubing. Holding the free end of the rubber tubing in an ordinary sterile test-tube, quickly plunge the needle into the most prominent vein; if expertly done, the patient will hardly feel it and the blood will immediately begin to flow. About 6 to 10 c.c. of blood is withdrawn and placed in the ice box over night to coagulate. The serum separates and may be pipetted off absolutely clear without cells. It is advisable to take the blood as far from a meal as possible,

as proximity to a meal makes the blood lipemic, interfering with perfect working conditions. (2) Having obtained 1 or 2 c.c. of clear serum, it is placed in a test-tube in the thermostat at 56° for one hour. Care must be taken not to permit the heat to rise too high (over 58°). (3) After this, 0.2 c.c. is placed in each of two test-tubes, one the test, the other the control. (4) To each is now added 0.1 c.c. fresh complement. (5) To the test portion is added one unit of antigen. The control does not receive any antigen. (6) Each tube receives now 3 c.c. of a 0.95 per cent. NaCl solution. In order to be able to judge properly the correctness of the procedure, the more controls one has the better; it is therefore necessary to compare the serum to be tested with two sera from known positive and negative bloods. (7) Shake every tube well and place in incubator at 37° or 38° for one hour. During this time, if the serum is luetic the antibodies present will, together with the antigen, bind the complement and render it inactive for hemolysis. (8) After one hour incubation each tube receives two units of amboceptor and 1 c.c. of a 5 per cent. suspension of sheep cells in 0.95 NaCl. The tubes are again vigorously shaken and placed in the incubator at 37° and inspected after ten minutes. If the reagents are properly adjusted hemolysis begins in the control tubes in fifteen to twenty minutes, and careful watching becomes a very essential point at this stage of the test. As soon as the control is completely hemolyzed the tubes are to be compared; only those should be pronounced negative that show a transparent fluid the same as the control.

Permitting the tubes to stand undisturbed in a cool place (15° to 17°) for twenty-four hours shows in the positive test a deposit of red cells, the size of the deposit depending upon the severity of the infection or proximity to the initial lesion as well as upon the degree of balance of the reagents used. Usually a markedly positive serum gives at the end of twenty-four hours a clear supernatant fluid of a light pink hue with a bordeaux red accumulation on the bottom of the tube. The weaker the reaction, the redder the supernatant fluid and the scantier the deposit of cells. In testing more than one serum, the reaction in each individual test must be considered as finished as soon as the controls are completely hemolyzed, in which case the two tubes are immediately removed to a cool place.

Technique of the Noguchi Reaction. *Principles Involved.* These are same as in the Wasserman, excepting that the amboceptor is directed against human cells, for reasons to be spoken of later. It also facilitates the handling of reagents, as they are mostly paper soaked in the antigen and amboceptor. These do not readily deteriorate, as is the case with fluid biological reagents. The serum does not need inactivation at 56°.

Modus Operandi. (1) With a capillary pipette allow one drop of fresh serum to fall into a narrow (1 c.m. lumen) test-tube. The pipette is not to be used for any other serum. (2) Add 0.05 c.c.

fresh complement. (3) To the front row (rear row for control) add one piece (more or less, depending on the titre) of antigen paper. (4) Prepare a suspension of human cells 1 drop of blood to 4 c.c. NaCl 0.95 per cent. It is best to prepare about 60 c.c. of NaCl solution and allow 15 drops of blood to fall from the experimenter's finger into the solution. The human cell suspension is placed over night in the ice box. Next morning the supernatant clear salt solution is pipetted off and a fresh quantity of NaCl is added (about 55 c.c.) to the cells in the beaker. Of this cell suspension add 1 c.c. to every tube in the rack. (5) Incubate for three-quarters or one hour at 38° or 39°, preferably in a large dish of warm water. Occasionally shake the tubes, to insure proper solution of the biological substance on the antigen paper. (6) Add to each tube (after incubation), front and back rows, one piece of amboceptor paper more or less, the quantity depending on the titre) and replace in the incubator, observing the result after ten minutes, and watching carefully the controls.

It will be noted in about fifteen minutes, more or less, that the rear row begins to get clear, and when complete transparency is obtained the test and control tube are to be removed to a cool place and observed. If the reaction is positive, then the front tube (test) will be opaque, in marked contrast to the control, which is transparent. For convenience of observation, I make use of a fine sealed tube (about 1 mm. in diameter) filled with black ink, which, when placed behind the control, will appear as a clear black line, whereas the positive tube will not show the black line, or it appears as a dim shadow—depending on the strength of the reaction.

It has been stated that a positive Noguchi test and a negative Wasserman is often due to the presence in the patient's serum of antisheep amboceptors. It is not necessary to perform this test with every serum as a control. Only sera giving the above results need be subjected to a verification. To demonstrate the antisheep amboceptor, place 1 c.c. of a 5 per cent. suspension of sheep cells in a test-tube, add 0.2 c.c. of patient's serum and 0.1 c.c. complement, add 3 c.c. of NaCl solution, place in incubator, and observe. If the amboceptor is present, the cells will dissolve and the mixture become transparent. The time consumed depends upon the number of amboceptor units present. I observed sera, capable of hemolyzing the cells completely in ten minutes.

Rationale of Controls. In the Wasserman and Noguchi reactions it is of vital importance to have every possible error excluded. For this purpose the controls used will answer. The substances to be controlled are the antigen, the amboceptor, and each individual serum.

The Antigen Control. This biological reagent, as is known, can per se inhibit hemolysis. To measure the degree of such interference, a tube containing a well-known normal serum (or, as I found just

as serviceable, no serum at all), plus antigen, plus complement, and antisheep amboceptor plus sheep cells ought to hemolyze in about twenty to thirty minutes. No reaction is to be considered as finished before the antigen control tube is completely hemolyzed.

The Amboceptor Control. Upon the efficiency of the antisheep amboceptor depends the rapidity of hemolysis of the sheep cells. It is therefore necessary to establish the amboceptor efficiency in a separate tube containing sheep cells, plus complement, plus antisheep amboceptor. It is not essential to add normal serum. The tube containing the above ingredients is always the first to hemolyze, requiring about fifteen to twenty minutes for a complete hemolysis.

Control for Each Serum. Every serum more or less has the power to interfere with hemolysis to a slight degree. In order to control the factor of individual inhibition, every serum tested is placed in each of two tubes, the front tube contains the antigen and all other biological reagents, the rear tube receives everything but the antigen. This shows the degree of individual inhibition as compared with the tube containing the amboceptor control.

Efficiency of the Entire System. For this a well-known luetic serum is utilized. The reaction is to be positive, and hemolysis should not occur in the front tube, even if exposed to incubation temperature for hours after the controls hemolyzed.

EQUIPMENT. At least one dozen or more of Mohr's pipettes, 1 c.c., graduated into $\frac{1}{100}$. One dozen 10 c.c. pipettes, graduated into $\frac{1}{10}$. One gross of ordinary test tubes. One gross of test-tubes 1 cm. in diameter, 12 cm. high. One-quarter dozen of graduated cylinders, 50 c.c.; $\frac{1}{4}$ dozen 100 c.c. Two 50 c.c. measuring flasks with glass stoppers. A few pounds of glass tubing, 5 mm. bore, to make capillary pipettes. One-half dozen test-tube racks for Wasserman tubes; $\frac{1}{2}$ dozen test-tube racks for Noguchi tubes. A piece of rubber tubing for tourniquet. One artery clamp for above. One dozen hypodermic needles, 19 bore. One thermostat regulated at 57° and one regulated at 37°. One electric centrifuge. Labels and pencil for writing on glass. One tall glass jar for flushing through used pipettes, height to be greater than any pipette used. One dozen Petri dishes. One dozen beakers, 100 c.c. capacity. Two fine forceps, and two Hagedorn needles. One package of quantitative filter paper. One razor (for killing guinea-pigs). One 15 c.c. Luer syringe.

PREPARATION OF ANIMALS. *Antisheep Amboceptors.* Several healthy rabbits (not less than four) receive every fifth day 1, 2, 3, 4, and 6 c.c. of well-washed sheep cells. This number of rabbits is used, as one or two may die during the injection weeks. The cells are obtained from the slaughter house and immediately defibrinated with a wire defibrinator or glass beads. In order thoroughly to wash the cells a high speed centrifuge is necessary, capable of making at least 3000 revolutions to the minute. Two of the cen-

trifuge tubes are filled with the fluid sheep blood, it being advisable, in order not to spoil the centrifuge, to have them of equal weight. The first centrifugalization brings the cells to the bottom, and the clear supernatant serum is pipetted off. The cells are now mixed with 0.95 per cent. NaCl solution and centrifugalized again, and the supernatant clear fluid is again pipetted off; this is repeated three times. The cells are now approximately serum-free. The entire quantity of cells in the tube is now brought up to its original volume with 0.95 per cent. NaCl solution, and of this, 2 c.c. is used for the first injection. With a sterile glass syringe this quantity is injected into the peritoneal cavity, having previously shaved and cleaned the puncture area. Cotton and collodion prevent wound infection. This procedure is repeated five days later with 4 c.c. of cells brought to its original volume, etc., until each animal has been injected five times. Nine days having elapsed since the fifth injection, the serum of the rabbit contains now a high lytic power against the red blood corpuscles of the sheep. The rabbit is killed and its serum used.

In the Wasserman reaction 1 c.c. of a 5 per cent. suspension of well-washed sheep red cells in 0.95 per cent. NaCl solution is the standard dose for each test. It is evident, therefore, that in order to test the power of our rabbit serum (antisheep amboceptor, as it is now called) we must use this quantity of sheep cells. Into each of six test-tubes is placed 1 c.c. of a 5 per cent. suspension of sheep cells in NaCl 0.95 per cent. These are marked from 1 to 6, and to each is added 0.1 c.c. of fresh guinea-pig serum (this is known as the complement serum and is the quantity used in the Wasserman test). We now add to test-tube (1) 1 c.c. of a 1 to 200 solution of our amboceptor. To test-tube (2) we add 1 c.c. of 1 to 400; to test-tube (3), 1 c.c. of 1 to 800; to test-tube (4), 1 c.c. of 1 to 1600; to test-tube (5), 1 c.c. of 1 to 3200. This is placed into the thermostat at 37° and the result noticed after fifteen minutes, thirty minutes, up to two hours. It will be seen that in fifteen minutes test-tube (1) is clearing up, or is clear (hemolysis); this would indicate that 1 c.c. of a 1 to 200 solution of our amboceptor is capable of destroying in fifteen minutes 1 c.c. of a 5 per cent. suspension of sheep cells. This proportion—1 to 200—is too strong, and may give negative results with some positive sera. The unit strength of the antisheep amboceptor is usually twice the quantity capable of hemolyzing the 1 c.c. of cells in two hours. If 1 to 1600 shows hemolysis after two hours and 1 to 3200 does not, then 1600 divided by 2 is the strength of the amboceptor, one unit equals 1 to 800. It is best to run two series of titration—one like the above, the second beginning with 1 to 250, 1 to 500, 1 to 1000, etc., so that a proper mean can be established and a more exact unit made. In table form the above is expressed as follows:

		Sheep cells.	Cells hemolyzed in
Tube 1 amboceptor = 1 to 200	Complement 0.1	5% 1 c.c.	15 minutes.
" 2 " = 1 to 400	" 0.1	" "	30 minutes.
" 3 " = 1 to 800	" 0.1	" "	50 minutes.
" 4 " = 1 to 1600	" 0.1	" "	1½ hours.
" 5 " = 1 to 3200	" 0.1	" "	2 hours.

Strength of 1 unit, 1 to 1600; dose for 1 test, 1 to 800. Date.....

A full-grown rabbit usually furnishes from 50 to 60 c.c. of serum. This is to be kept in a glass-stoppered flask in the ice box (lower compartment). The hemolytic power does not indefinitely remain the same as in the beginning; it is, therefore, necessary to establish the titre at least once every week, and to make up the dilutions accordingly. These dilutions are to be prepared on the day of testing. The rabbit serum does not have to be inactivated to get rid of the complement in it, as the quantity of serum used is too small to influence in any way the resulting outcome of the test.

Preparation of Complement. A full-grown guinea-pig is held over a Petri dish, and after having it narcotized, the bloodvessels of the neck are severed with a razor. Suspended by the hind legs the animal is exsanguinated, and the collected blood is permitted to remain at room temperature for at least three hours. The serum collects in large drops and may be pipetted off, or the coagulum plus the serum is placed in a centrifuge tube and after five minutes centrifugalization the supernatant serum is pipetted off into a sterile test-tube; but such a serum is not as reliable as when left for three hours with its cells. About 6 c.c. of complement is obtained from one guinea-pig.

Preparation of Sheep Cells. Obtained from the slaughter house, the cells are washed three times with 0.95 per cent. NaCl solution, and 1 or 2 c.c. is mixed with 20 or 40 c.c. of salt solution, making a 5 per cent. suspension of cells.

Preparation of Antigen. The fresh liver of a luetic fœtus or the liver of any baby cadaver is chopped up very finely, and the mass is spread on a few Petri dishes and dried. The drying process is hastened by a current of air produced by an ordinary electric fan. Lately, not only baby livers, but also the livers of dogs, the hearts of guinea-pigs, and other organs were used to make antigen. The usefulness of the antigen is only established when in actual standardization it is found serviceable and works faultlessly with decidedly syphilitic and unquestionably normal sera. Consequently it makes little difference whether one uses the extract obtained from the liver of a syphilitic fœtus or from the heart of a guinea-pig, provided they are well titrated.

It is better—according to German workers—to use more than one extract, and have a series with well standardized luetic liver antigen,

one with guinea-pig heart, and another with dog liver, or normal human liver. To proceed with the making of antigen the obtained dried liver is rubbed into a powder and kept in an exsiccator over $CaCl_2$ in a cool, dark place. According to Tschernogubow, such a powder is serviceable for a very long time. Of this powder, 0.5 gram is extracted at room temperature or in an ice box with 25 c.c. of 95 per cent. alcohol for twenty hours, then filtered, and the filtrate used for experiments.

For the actual Wasserman test, one part of this opalescent filtrate is diluted with five parts of 0.95 per cent. NaCl, and 0.5 to 1 c.c. used for each test-tube, the dose depending upon the established titre. The above process extracts from the liver substances soluble in alcohol, chiefly bodies of a fatty nature (lipoids). There are other means of obtaining lipoids, the above being one of the simplest, having also in view the preservation of the antigen in an active form. The liver, instead of being dried and powdered, may be directly extracted with five volumes of absolute alcohol, and the extract obtained by driving the alcohol off at a temperature not higher than 40° C. or with the electric fan. The obtained extract is much more powerful than the above, is soluble in ether, from which NaCl solutions are made for use. The titre is established carefully as follows:

Titration of Antigen. The unit dose of antigen must be of such a strength that one unit will completely inhibit hemolysis of 1 c.c. of a 5 per cent. suspension of sheep cells, with 0.2 c.c. of a known luetic serum plus 0.1 c.c. of complement; provided double this dose does not interfere with the complete hemolysis of cells using a known normal serum and complement.

TABLE OF ANTIGEN STANDARDIZATION.

Luetic Series. Each tube contains syphilitic serum, 0.2; complement, 0.1; cells, 1 c.c. 5%: amboceptor, 2 units.		*Normal Series.* Each tube contains normal serum 0.2, complement, 0.1; cells, 1 c.c., 5%; amboceptor, 2 units.	
			Hemolysis.
Tube 1, Antigen, 0.025	1 hour 15 min.	Antigen, 0.025	15 minutes.
" 2, " 0.05	1 " 25 "	" 0.05	15 "
" 3, " 0.075	2 " 50 "	" 0.75	15 "
" 4, " 0.10 }	No hemolysis after	" 0.10	20 "
" 5, " 0.15 }	24 hours in incu-	" 0.15	30 "
" 6, " 0.20 }	bator.	" 0.20	35 "

Dose of one unit, 0.1 c.c.

From the above facts it is evident that the dose next to the largest hemolyzing dose is the strength of one unit, or 0.1 c.c. It is also apparent that 0.2 c.c., or a double dose, will not inhibit hemolysis when used with a normal serum.

In establishing the unit dose of antigen as well as antisheep

amboceptor it is of utmost importance to titrate two or three times in order to get as uniform results as possible, and only uniform work will enable one to come to a proper conclusion as to which is the necessary dose. For establishing the strength of the antigen and amboceptor, well-known fresh luetic and normal sera are to be used, as well as fresh suspension of cells and fresh complement.

Before using the standardized reagents it is advisable to perform two or three actual tests with well-known positive and negative sera. After this the substances may be considered safe for use. The above lines will give one a fair idea concerning the preparation of the biological reagents for the Wasserman reaction. For the Noguchi reaction it will be necessary, first, to acquaint the reader with the principles involved, and then the preparation of reagents will follow.

PRINCIPLES OF THE NOGUCHI TEST. Workers with the Wasserman reaction often could not explain why a positive result could not be obtained with some true luetic sera. Later it was demonstrated that this was due to the presence in the human serum of substances capable of dissolving the red blood corpuscles of the sheep; in other words, some human sera contained antisheep amboceptors. From an analysis of the workings of the Wasserman test, one could offer an objection to the statement by pointing out the fact that even in the presence of natural antisheep amboceptors, there would be no complement to bring about lysis in the hemolytic system, for the complement has been bound up in a luetic serum by the antigen. This is certainly true to some extent, but it is also true that in the presence of an excess of amboceptors, a very small quantity of unbound complement will suffice to bring about complete solution of the sheep cells used in the test. Now we very well know that in performing the Wasserman reaction we are dealing with an unknown quantity, this unknown quantity being the number of syphilitic antibody units (or some substance capable of binding complement with the antigen) present in the luetic serum. It needs no comment that the stronger and more virulent the infection, the greater the number of such bodies in the serum and naturally the firmer and more complete the binding of the complement. Sometimes the quantity of antibody is so small that a goodly portion of the complement escapes unbound and does its work by bringing about partial hemolysis; this is the condition of affairs taking place in some weak reactions. If such a serum contained antisheep amboceptors, they would have enough complement to cause hemolysis and render the result negative.

An old experiment of Ehrlich and Morgenroth proves that the greater the number of amboceptor units, the smaller the quantity of complement necessary to bring about complete hemolysis. If the patient's serum contain 10 or 20 units of antisheep amboceptor, and if only $\frac{1}{10}$ or $\frac{1}{20}$ of a unit of complement escapes deviation, this

quantity will prove amply sufficient to cause hemolysis. In the Noguchi test this cannot take place, for the hemolytic system used consists of human cells plus antihuman amboceptor, and, naturally, the human organism does not contain antihuman amboceptors. Luetic sera containing antisheep amboceptors will give a negative Wasserman but a positive Noguchi test.

PREPARATION OF REAGENTS. *Antihuman Amboceptor.* Rabbits are injected with human cells the same as the sheep rabbits. After nine days the rabbits are killed, their serum collected and disposed of as follows: The fluid amboceptor loses strength on standing, so much so that it may not contain one-fourth of its original power a month after the first titration. In a dry state it can be used for a very long time without losing its strength. I prepare my antihuman amboceptor by cutting quantitative filter paper in 5 mm. squares. These squares are stuck on to pins fastened to a cardboard. With a very fine capillary pipette (as fine a one as can be made) one drop is blown on each piece of filter paper and placed in the thermostat for drying. In half an hour the papers are dry and fit for use. By this mothed each square receives exactly the same quantity of serum, and is not subject to differences in dissemination which must be considered when the serum is blown on a larger piece of filter paper and cut subsequently in 5 mm. squares. My method takes longer, but the difference is worth while, for each square holds exactly the same quantity of amboceptor. My present amboceptor is two and one-half months old and as good as new. In my work I find one piece of this amboceptor serviceable.

TITRATION OF ANTIHUMAN AMBOCEPTORS.

	Human cells 1 drop to 4 c.c. NaCl.	Complement.	Hemolysis in
Tube 1, Amboceptor, ½ piece	1 c.c.	0.05	2 hours.
" 2 " 1 "	1 c.c.	0.05	20 "
" 3 " 1½ "	1 c.c.	0.05	11 "
" 4 " 2 "	1 c.c.	0.05	8 "

As a result of five months' work with the Wasserman and Noguchi tests, I am enabled by this time to give a fair opinion as to its uses. Shortly stated, the two reactions are to my mind of the foremost importance to the clinician, and so far as accuracy is concerned, they almost occupy the first place among our means of detecting disease. The above statement is not at all to be marked as enthusiastic, for I must admit that six or eight weeks of work was spent on a very rough road to overcoming difficulties and getting acquainted with the peculiarities of the reaction, differences in the bloods submitted for tests, changes in the biological reagents, etc. My first

300 tests contained about 30 per cent. error, which by steadfast application and constant research into the causes for these mistakes, enabled me to weed them out to such an extent that now, after five months' work, I am in a position to report in 100 luetic sera, 98 to 99 positive results. In the following lines will be given the means of arriving at such a degree of precision.

First, no one who has worked with the Wasserman reaction alone has a right to claim infallibility. This is especially true for the first two months of work. Constant application and undivided attention are the prequisites for thoroughness, and only such workers are to be depended upon for their results. I believe it to be almost impossible to arrive at a high degree of technical skill without the above conditions. The handling of pipettes, even by laboratory workers, has to be improved and rendered faultlessly exact, for a drop more or less may sometimes mean a false diagnosis. As to the use of the Wasserman test alone, without the Noguchi modification, I would consider as lacking in proper controls, for, as stated before, the Noguchi modification eliminates the possibility of a negative result when antisheep amboceptors are present; and permit me to emphasize that they are present quite frequently, being the *raison d'être* of negative results in about 8 or 9 per cent. of Wasserman tests with luetic sera. Using the Noguchi test with the Wasserman places one on a much surer footing, and not only gives one better results, but also enables the worker to detect inaccuracies in the biological reagents used in the Wasserman tests.

As mentioned before, the Wasserman reaction gave a negative result in 8 or 9 per cent. of syphilitic sera. This rather undesirably high percentage of error was reduced to 1 or 1.5 per cent. when using the Noguchi and the Wasserman combined. It became apparent from the first 100 or 150 reactions that the Noguchi test, besides giving a positive reaction with all luetic sera (99 times out of 100), will sometimes give a positive reaction with a negative serum, and this to an extent of 7 per cent. As alarming as such a high degree of inaccuracy may at first sight appear, it becomes irrelevant when used with the Wasserman reaction. I have formulated a system of recording the results, which, at a glance, will give the proper interpretation of the findings in the two methods. The table is an outcome of 1400 reactions, and with it 98.2 of correct interpretations were obtained. Let me impress upon the worker the necessity for more than one test on each patient. I never render a decision after one test. Always perform two Wasserman and two Noguchi tests on different days, using the same serum. It is also to be borne in mind that a fairly marked Wasserman reaction, 99 times out of 100, means syphilis, and that a negative Noguchi the same number of times means no syphilis. The two methods are very decisive, but in opposite ways; and used together, carry with them an assurance which no amount of thoroughness and precision

will replace if only one method is used. I, therefore, recommend, and am sure will be supported by other workers, that the Wasserman reaction is much less conclusive when performed without the Noguchi test, and that in the combination of the two methods we really possess a very valuable diagnostic aid.

TABLE OF INTERPRETATION OF RESULTS.

	Wasserman test first day.	Noguchi test first day.	Wasserman test second day.	Noguchi test second day.	Opinion formed.
1	S+	S+	S+	S+	Unquestionably syphilitic.
2	+	+	+	+	Unquestionably syphilitic.
3	+	—	+	—	This happens rarely, and if technique is correct, means positive. Should be done three times.
4	—	+	—	+	If antisheep amboceptors are present = positive; if no antisheep amboceptors are present = negative. Should be done three times.
5	—	W+	—	+	Suspicious. Must be decided clinically
6	—	W+	W+	W+	Positive, but weak.
7	—	S+	—	S+	Some fault with the reagents in Wasserman test, unless antisheep amboceptors are demonstrated, then positive.
8	W+	+	—	W+	= positive.
9	—	W+	—	W+	= negative, even if antisheep amboceptors are demonstrable.
10	—	+	—	—	= negative.
11	—	—	W+	+	Faulty technique. Repeat twice.
12	W+	W+	—	—	= negative. Repeat.

S+ = strongly positive. + = ordinary reaction.
W+ = weakly positive. — = negative.

The above table is compiled from numerous actual observations, and is not influenced by the personal equation of the worker. To eliminate this factor, I have performed the last few hundred tests without a knowledge of the patient's condition. In many instances the test-tubes with the patient's blood were given me bearing only a number for identification, and only after rendition of the final result was the clinical diagnosis revealed to me. On one such occasion 12 sera out of 18 reacted positively, and proved to be from 11 cases of tabes and one of tricuspid stenosis. The latter subsequently reacted ten times positively. Such non-knowledge of the patient's condition is to be recommended if one wishes unbiassed results; and statistics obtained by such means are far more valuable than those obtained by giving the laboratory worker the diagnosis with the blood. The clinical findings belong to the doctor, and ought to be offered in exchange for the laboratory report, and not sooner.

This work comprises results from 1390 analyses. The first 300

are unreliable on account of lack of technique. The remaining 1090 carry with them a high degree of precision. Analyzing the sensitiveness of each method independently, I find that out of 503 sera examined by the Noguchi method, 43 were contrary to the diagnosis of expert clinicians. Of these 43 probably incorrect results, 35 were interpreted as positive and 8 as negative. The Wasserman reaction behaved as follows: Out of 487 sera, 37 were wrong. Of these 37, 30 were negative and 7 positive. Using the combined method of reading results—having performed two Wasserman and two Noguchi tests and then rendering a report—the results were as follows: Out of 487 reports, 9 were contrary to the clinical picture; of these, 5 were negative and 4 positive, making it less than 2 per cent. error.

Before giving my conclusions, I would like to offer a few explanations of the peculiarities and at times perplexing results obtained while working with complement deviation. On more than one occasion the presence of antisheep amboceptors has been blamed for a negative Wasserman reaction. This is true only to a certain extent, for we know that in the presence of a sufficient quantity of syphilitic antibody, a perfect and complete deviation of complement will take place with a well-standardized antigen. The antisheep amboceptor comes into prominence only when there is a paucity in luetic antibody, and then only will render the Wasserman reaction useless.

Some guinea-pigs furnish a serum which is very poor in complement, rendering the amboceptor powerless or too weak to hemolyze the given quantity of cells; in such a case the outcome is a weak positive reaction in a negative serum.

The sheep cells must also be considered, as they, too, have varying powers of resistance to the amboceptor, and will sometimes remain intact for hours. This is one of the reasons why some controls and tests react very sluggishly. Another reason for a prolonged resistance to the amboceptor is the presence in the patient's serum of anticomplemental substances which hinder or render inert the completing function of the complement. In such a case the addition of another half dose of guinea-pig serum will bring out clearly the nature of the serum, and also decide its luetic or negative qualities.

Although the above deviations cause delay, puzzle and discourage the beginner, by far the greatest source of error lies in the worker himself, especially when a drop more or less is considered as insignificant, or any pipette as clean enough. Thorough cleanliness, using sterile dry pipettes and containers, as well as faultless pipettation, are conditions *sine qua non* in the performance of the Wasserman and Noguchi tests; they are only acquired after weeks of constant work and application. I do not wish by these statements to discourage anybody from working with the methods, but I would advise the worker not to place himself on record before every detail

has been mastered and he is able to answer why and wherefore certain tests were negative on one occasion and again positive on another day, and which of the two is correct. The laboratory worker, being responsible to the clinician for his statements, ought to be in a position to help him considerably, but only when his work has been carried out very carefully, unbiassed by personal opinion, and submitting the result of a delicate test as read from the test-tube. I do not believe we are as yet in a position to say that a serum preventing the hemolysis of sheep cells in the Wasserman test, or human cells in the Noguchi modification, means the presence of syphilis. Leprosy gives it, trypanosomiasis is reported to give the reaction, and undoubtedly, there are other conditions which give rise to the formation of substances in a patient's serum which, when brought in contact with antigen (lipoid bodies), are capable of inhibiting, destroying, or deviating the completing action of the complement, so that hemolysis will not take place when a specific hemolysin and cells are placed in such a mixture. I had occasion to analyze two cases of scleroderma, and found in both the reaction positive. Whatever the process may be, the explanation of its modus operandi is still a theory made to fit the well-known exposition of Ehrlich's concerned in immune processes, which in itself is only an ingenious theory. The practical man wants a reliable report on the blood submitted for analysis. In my case, only yes or no was accepted. I was confronted with questions as to the significance of a weak reaction, an ordinary and a strong reaction. From the above remarks it is apparent that one is hardly justified to state positively that even a strong reaction signifies, without the least doubt, syphilis. In the vast majority of bloods syphilis is most likely the cause for a strong reaction, but it need not at the same time be the only factor responsible for its appearance.

A strong reaction naturally carries with it a greater degree of assurance in rendering a decision than a weak reaction. This is especially true of the Wasserman test, for at no time was a strong reaction obtained with this method unless the blood came from a patient giving clinically or anamnestically signs of syphilis. A strong positive reaction with the Noguchi test is much less significant, at least in my experience. I obtained positive results with the Noguchi method when, from the physical examination and the history, syphilis could be excluded to the satisfaction of the clinician. On the other hand, a distinctly negative result, using the Noguchi method, is very valuable, and in the majority of instances comes from an individual free from a syphilitic taint, as corroborated subsequently by a careful examination.

In the above work no deviation from the accepted technique was resorted to. In the Noguchi tests personal communication with the originator of the method greatly facilitated the progress of my work by rendering clear some obscure phenomena and furnishing a re-

liable antigen. The amboceptor I prepare myself by a slightly different method, the aim being greater uniformity in the 5 mm. squares of paper used in the tests. In every other detail the technique is exactly as advocated by Dr. Noguchi, using the same reagents, and working with the same controls.

CONCLUSIONS. 1. Every beginner, for the first month or two, will obtain unsatisfactory results from lack of proper technique.

2. Having mastered the technical difficulties, always perform another test for verification.

3. Acquire the habit of working with two methods, the Wasserman and Noguchi.

4. Every week or ten days, spend a day in standardizing reagents.

5. With proper technique and well balanced reagents it is possible to report correctly in 98 per cent. of cases.

6. Questionable reactions are not to be used for diagnosis, and if a given serum does not react strongly after a number of repetitions of the tests, the diagnosis is to be left to the clinician.

7. I find that the Wasserman reaction gives negative results in about 7 per cent. of positive sera, treatment periods excluded.

8. The Noguchi method gives 8 per cent. of positive results in clinically well-established non-syphilitic individuals. The positive reactions in these cases are ordinary reactions, and cannot be said to be remarkably strong.

9. Exceptionally strong reactions are obtained in untreated cases of general paresis with both tests, as well as in primary sores four weeks after infection.

10. With time, the antibody content of the serum diminishes. The antibody content also diminishes during inactivation to about one-third. (Personal communication by Dr. Noguchi.)

11. The table of interpretation of results was of great help in rendering many correct reports, and served to some extent as a guide in the disposal of the serum submitted for testing.

12. The compilation of this table took place after analyzing the results from 1390 reactions.

13. I do not feel justified to place myself on record concerning the specific or non-specific nature of certain diseases. However, the majority of sera from tabetics (78 per cent.) and most sera from general paretics (not treated recently) deviate complement, and the latter most strongly. In diabetics a positive result could rarely be had. The few cases of aneurysm and aortic lesions as well as one case of tricuspid stenosis, all gave a positive result. Out of 84 locomotor ataxia cases, 66 gave a positive Wasserman and 70 a positive Noguchi reaction. The findings in clinical conditions will be the subject of another communication.

14. I am not at present in a position to state the influence of treatment on the reaction, and to what extent or manner my method of interpretation will be influenced.

I wish to thank all gentlemen who were helpful in furnishing material for work, my gratitude being due to Dr. I. Abrahamson for initiating this work in the Montefiore Home Laboratory, to Dr. Noguchi for his generous help in elucidating complex phenomena and furnishing some reagents, and to Drs. H. Brooks and S. Wachsmann for encouraging and facilitating the research.

A STUDY OF THE ALLEGED PRESENCE OF TUBERCLE BACILLI IN THE CIRCULATING BLOOD.

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Twelve months have now elapsed since Rosenberger[1] read his initial paper before the Pathological Society of Philadelphia, upon the presence of tubercle bacilli in the blood. This paper gave rise to considerable enthusiasm in local medical circles and no little interest to the medical world at large, because he asserted that it was easily possible to demonstrate the presence of tubercle bacilli in the blood of every case of tuberculosis, by means of a technique so simple that it became a matter of surprise that previous efforts, along this same line, by many competent investigators, should not long ago have been rewarded with equal success. Many accepted his findings quite readily, while others listened to them with a good deal of reservation.

Rosenberger's original studies comprised 50 cases divided as follows: 2 cases of fibroid tuberculosis; 1 case of pneumothorax; fifteen cases of incipient tuberculosis; 23 cases of advanced tuberculosis, and 3 cases of the laryngeal form of the disease. He has since augmented this number, so that at the present time they embrace over 300 observations, including cases of lupus. In all of these cases he has met with the same success, finding the bacillus in the blood in every instance.

This contribution was immensely important, because, if correct, some of our preconceived ideas concerning tuberculosis must be modified, and because it would afford the clinician a simple and almost infallible means of diagnosticating the malady in its earliest incipiency, a matter at the present time perplexing and difficult, if not impossible. In lieu of all this it is astonishing to find that, with the exception of two brief contributions on the subject, Rosenberger's observations have not been confirmed.

In reviewing the literature in the chronological order in which

[1] Amer. Jour. Med. Sci., 1909, cxxxvii.

the reports have appeared, the following are noted: Forsyth reports the study of 12 cases, with positive results in 10. Burnham[2] and Lyons[3] detailed their observations in 10 cases—negative in every instance. Schroeder and Cotton[4] published the results of their studies of the blood of 48 tuberculous cattle, with findings uniformly negative. Mohler,[5] carrying on an independent investigation, examined the blood of eight tuberculous cattle with negative results. Ravenel and Smith[6] state that they have examined the blood of 18 cases, and have been unable to demonstrate tubercle bacilli in any of them. Petty and Mendenhall[7] studied 10 cases, only 7 of which were tuberculous, and in all of them bacilli were demonstrable in the blood. One case of axillary adenitis, presumably tuberculous in nature, but subsequently shown by the pathologist to be sarcomatous, gave a negative result. The two remaining cases, it is to be inferred, were cases of enteric fever; but in both of them acid-fast organisms supposed to be tubercle bacilli were found in the blood.

Hewat and Sutherland[8] made twenty-two examinations of twenty tuberculous individuals, and in one case only were they able to demonstrate acid-fast organisms. However, in repeating the examination of the patient's blood in which two acid-fasts were found in the initial test, it was negative, which led the authors to believe that the presence of the organisms was due to incidental contamination. Anderson[9] examined the blood of 48 cases of human tuberculosis together with 13 guinea-pigs and 8 rabbits experimentally infected by the Rosenberger method. Of these, but one, a case of human tuberculosis, revealed acid-fast organisms in the blood specimen; but inasmuch as guinea-pig inoculation was negative, Anderson does not think that the organisms found were tubercle bacilli. It is of interest to note that in 3 of the rabbits cultures were successfully grown from the blood, and this in face of the fact that it was impossible to demonstrate the organisms by smear in the blood of these animals.

In this preliminary report is added a study of 56 cases, in the blood of which tubercle bacilli were sought with the utmost pains. The cases were divided as follows: Five cases of suspected tuberculosis in which the physical examination was negative or questionable; 10 cases in which physical examination was clearly positive, but in which the sputum was either negative or was not examined; 4 incipient cases in which both the physical examination and the sputum were conclusive; 9 cases moderately advanced; 1 moderately advanced case complicated with laryngeal tuberculosis; 1 case of

[2] Brit. Med. Jour., 1909, i, 1001.
[3] Jour. Amer. Med. Assoc., 1909, liii, 731.
[4] Bulletin No. 116, U. S. Department of Agriculture.
[5] Ibid.
[6] Jour. Amer. Med. Assoc., 1909, liii, 649.
[7] Ibid., 1909, liii, 867.
[8] Brit. Med. Jour., October 16, 1909.
[9] Bulletin No 57, Hygienic Laboratory, United States P. H. and M. H. S.

tuberculous adenitis; 1 case of miliary tuberculosis in an infant; 1 case of bilateral senile pneumonia; and lastly, 2 cases of epidemic cerebrospinal meningitis.

Particular interest was aroused through the appearance of Rosenberger's paper, because before its appearance a similar independent investigation was in progress at the Henry Phipps Institute, the technique employed differing but little from that of Rosenberger. The work had been abandoned, however, after the careful study of the blood of 8 cases of undoubted tuberculosis was productive of negative results only. The technique was as follows: 5 c.c. of blood was withdrawn from any convenient vein and immediately added to an equal quantity of a 2 per cent. solution of sodium citrate. The mixture was then centrifugalized for ten minutes in a rapidly revolving electric machine, the supernatant fluid pipetted off, distilled water added to the sediment, the mixture vigorously shaken and recentrifugalized. The sediment thus laked was withdrawn with a pipette, thick smears made on clean glass slides, fixed, and stained for five minutes in carbol fuchsin, decolorized in 5 per cent. nitric acid in 95 per cent. alcohol, and counterstained for five seconds in borated methylene blue. Rosenberger at first employed the centrifuge but subsequently discontinued its use, as he thought it gave less satisfactory results than simple sedimentation. On the other hand, Forsyth employed the centrifuge, which in his hands gave better results.

Rosenberger's technique as given in his original article, was rigidly followed in my latest series of cases. It requires that the blood, after being drawn and agitated with a citrate solution, be allowed to sediment for twenty-four hours in a refrigerator, at the end of which time the sediment is pipetted off and thickly spread upon clean glass slides, which are then placed on a copper plate and subjected to a low degree of heat until dry. They are subsequently laked by placing them in a jar of distilled water and the resulting thin, almost colorless film dried and fixed by rapidly passing through a Bunsen flame. They were next stained, carbol-fuchsin with Pappenheim's stain as a decolorizer and counterstain being employed. In the first fifteen examinations this technique was employed exactly, but Pappenheim's solution was eventually discarded because it gave rise to so many confusing artefacts. Indeed, in a large majority of the slides so stained these were met with and were sometimes so deceptive in their resemblance to tubercle bacilli that co-workers in the laboratory who were asked to examine them frequently differed in their judgment. The fact, however, that after the Pappenheim stain was abandoned, and decolorization in acid alcohol with counterstaining in borated blue substituted for it, no such bodies were encountered would, I think, seem to prove that they were artefacts.

In the initial part of the investigation six slides were made from

the blood of each case and each examined critically field by field, but after 7 cases had been so studied it was deemed sufficient that two slides be prepared, and from thirty minutes to three hours devoted to a study of each of them. Singularly enough, in the few cases in which acid-fast organisms were demonstrable they were found in less than fifteen minutes. In one case only three minutes were required, in another it required only eight minutes' search to discover the first group of bacilli, and a second group was discovered on the same slide after twelve more minutes. In studying another slide, only thirteen minutes were required to find a group of organisms, which were the only ones met with, although another half hour was expended in attempting to locate more. Bacilli were found in six minutes in another case, and a few others after twenty-three more minutes. Lastly, one and a half minutes was all the time required to demonstrate them in another case.

The cases which gave positive results were five in number, and, remarkable though it may seem, with two exceptions were not cases of tuberculosis. As a matter of fact, if the case of miliary tuberculosis in the infant and one suspicious case of incipient tuberculosis be excluded, every case of tuberculosis examined gave a uniformly negative result.

The 5 cases referred to as being positive were as follows: One case of miliary tuberculosis; 1 case of suspected incipient tuberculosis; 1 case of senile bilateral pneumonia; and 2 cases of epidemic cerebrospinal meningitis. The finding of acid-fast organisms in the blood of the cases of cerebrospinal meningitis was of so much interest that it may not be amiss to enter a little into detail regarding them, because it proves how readily the clinician could be—and was for a time—led astray in his diagnosis by such laboratory findings.

Case I.—W. B., a student in one of the colleges of the suburbs of Philadelphia was admitted to the Bryn Mawr Hospital with a history of headache and malaise for three or four days prior to admission. The headache was very intense, pyrexia was present, the pupils were dilated, and he complained of some abdominal pain. At times he talked incoherently. His neck was very slightly rigid, with no pain on movement. There was anesthesia of the cornea. No rose spots were demonstrable. The attending physician suspected enteric fever, although a tentative diagnosis of meningitis was made. A Widal test was negative, and a leukocyte count of 10,200 was obtained. A lumbar puncture being refused, 10 c.c. of blood was withdrawn from an arm vein, 5 c.c. of which was utilized in making a blood culture for the purpose of demonstrating typhoid bacilli if possible, the other 5 c.c. being mixed with a citrate solution to be examined for tubercle bacilli. On the following day the patient's symptoms had become intensified. He was now delirious, there was marked rigidity of the neck, and herpes labialis

appeared. Lumbar puncture was still refused. Examination of the blood on this day showed acid-fast bacilli, and in the absence of any epidemic of cerebrospinal fever, a diagnosis of tuberculous meningitis with miliary tuberculosis was made.

CASE II.—P. B., a college chum and room-mate of W. B., was admitted to the same hospital on the day that the diagnosis of Case I was supposed to have been cleared up. He also had marked meningitic symptoms—delirium, retraction of the neck, and the characteristic decubitus assumed by such victims. Kernig's sign was marked. Becoming ill so soon after his room-mate and with similar symptoms, it was suspected that both young men were the victims of the epidemic form of cerebrospinal meningitis, and a lumbar puncture was performed. The fluid obtained was purulent, and upon microscopic examination showed innumerable diplococci with the morphological and tinctorial characteristics of the meningococcus. No acid-fast bacilli were found, though they were carefully searched for. A lumbar puncture was now done in Case I, and meningococci were also found, but again no acid-fast bacilli could be discovered in the spinal fluid. As a matter of interest, 5 c.c. of blood from Case II was secured and examined for tubercle bacilli, and to the writer's surprise a few acid-fast organisms were demonstrated.

True, there is a possibility that both of these patients were tuberculous, though it must be admitted that it would be a peculiar coincidence. We must also remember that Rosenberger claims to have demonstrated acid-fast bacilli in the blood of apparently healthy individuals. Might the blood of these two individuals have revealed acid fast bacilli had such an examination been made prior to their falling ill? Petty and Mendenhall found acid-fast bacilli in the blood of two of their patients who were apparently suffering from typhoid fever. Be that as it may, the point is, that even though acid-fast bacilli were demonstrable in the blood, it could scarcely be regarded as definite proof of the existence of tuberculosis. Had Case II not contracted the disease, W. B., dying as he did after a protracted illness, would have been considered a case of tuberculous meningitis with miliary tuberculosis, and a death certificate issued accordingly, when, as a matter of fact, he was not a victim of either disease. P. B. died also, and it might be added that an autopsy, though urgently sought for, was refused in both instances. No postmortem examination was, unfortunately, permitted in the case of bilateral pneumonia, in whose blood acid-fast organisms were found. The patient was a woman, aged sixty-five years, whose clinical symptoms were characteristic. Repeated examinations of the sputum never showed the presence of tubercle bacilli, though pneumococci were found in abundance.

The 50 cases of tuberculosis, the study of which form the basis of this paper, were ward and dispensary patients at the Henry

Phipps Institute of Philadelphia. In every case the blood was secured by introducing a needle into a vein, and the staining performed according to the technique already given. Careful examinations were made, and with a single exception were uniformly negative. The one patient in whose blood acid-fast organisms were found presented no physical signs whatsoever, though her history was suspicious. Two separate groups, one of five and one of three acid-fast organisms, were found in the blood of this case. They were not typical for the tubercle bacillus. In fact, in no case have the organisms discovered been morphologically typical. In some instances they appeared much larger and broader with round ends and a pale pink color; in other instances they were short and stained intensely. None showed irregularity of staining, and in no case was clumping observed. The bacilli found in the case of W. B. were chiefly of the large, broad type, and peculiar in that one group of the organisms were in chain formation, two chains lying parallel, one consisting of five elements, the other of four.

Inoculation Experiments. In order that the character of the organisms might be more accurately investigated, inoculations of guinea-pigs with the blood was used as a control. Approximately 2 c.c. of the blood from each of 37 of the 50 cases of tuberculosis was inoculated into guinea-pigs. In the first 21 animals the injection was made intraperitoneally, but as it was suggested that the peritoneal fluids might possibly exert some bactericidal influence, the subcutaneous method was substituted for the remainder. Two pigs were inoculated from each case, 74 animals being thus utilized; 17 died prematurely—under three weeks. Of the remainder, 13 survived the injection from two to seven months; 14 from from one to two months, and 5 approximately three weeks. All were carefully autopsied, and in no single case was there any macroscopic evidence of tuberculosis, glandular or otherwise. The failure to induce the disease in guinea-pigs by injecting them with the blood from tuberculous individuals is supposed by Rosenberger to depend upon the attenuation or death of the organisms in the blood stream. The experiments of Liebermeister[10] are, however, convincingly opposed to this view.

Sources of Error. That Rosenberger should report constant positive results in a large series of cases, and that Ravenel and Smith, Cotton and Schroeder, and Mohler uniformly negative ones, and that negative results should occur in the 50 cases herein reported, is, to say the least, extremely perplexing. To say that the organisms are only present in the blood at certain stages of the disease is not tenable, because Rosenberger found them at all stages. How, then, are such discrepancies to be accounted for? All sources of contamination seemed to have been excluded by

[10] Centralb. f. allg. Path. u. Path. Anat., 1908, xix, 934.

Rosenberger in his investigation, but Burnham and Lyons, and more recently Brem, have demonstrated at least one source through which error can arise. Brem,[11] intent upon confirming or refuting Rosenberger's work, and finding acid-fast bacilli fairly constantly, although his inoculation experiment in guinea-pigs proved negative, was led to suspect the water he made use of for his solutions and also his chemicals and stains. All were critically examined for the presence of the acid-fast organisms, but with no result until at last, after fixing the sediment from the distilled water upon a slide by means of albumin, he was able to demonstrate acid-fast organisms in greater or less numbers in every specimen examined. It is true that Rosenberger examined his solutions and also with negative results, but as Brem points out, the failure to find the water bacilli may have been due to the fact that no albuminous material was used as a fixative. Both at Bryn Mawr Hospital and at the Henry Phipps Institute the water used for making the various solutions is distilled from a Jewell apparatus. Inasmuch as of the five positive findings four were from cases in the Bryn Mawr Hospital, some contaminating factor was suspected. The water had already been examined and no acid-fast organisms discovered, for the very reason that may have led Rosengerger into error, namely, the lack of a fixative, for when the sediment from the distilled water at the Bryn Mawr Hospital, where the bacilli had been found, was examined many acid-fast organisms were discovered, and when the water at the Henry Phipps, where practically no bacilli had been found, was examined, no acid-fast organisms were found. In summing up, it seems clear that tubercle bacilli do not constantly circulate in the blood of tuberculous individuals, though they are occasionally present, as is shown by the inoculation experiments of Liebermeister. Being very few in number, they must be extremely difficult to find, otherwise out of 50 cases so carefully studied some should have revealed themselves.

IS THROMBO-ANGIITIS OBLITERANS RELATED TO RAYNAUD'S DISEASE AND ERYTHROMELALGIA?

By Leo Buerger, M.D.,

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In March, 1908, in a preliminary communication, I presented to the New York Pathological Society the results of my studies on the vessels of cases of so-called endarteritis obliterans. At that time I demonstrated that the lesions of endarteritis obliterans of the lower

[11] Jour. Amer. Med. Assoc., 1909, liii, 909.

extremities (or, as the Germans call it, *Spontan-Gangrän, Angiosklerotische gangrän*) are not due to proliferation of the intima, but are thrombotic in nature; that, in this disease, there is extensive obliterating thrombosis in the arteries and less often in the veins of the lower extremities, followed by organization and canalization with an attempt at the production of sufficient collateral circulation. I, therefore, suggested that the names *endarteritis obliterans* and *angiosclerotic gangrene* be dropped in this connection, and that the term *thrombo-angiitis obliterans* be employed.

My investigations at that time were particularly aimed at throwing light on the pathology, although I had already collected notes on the symptomatology of more than twenty-five cases. Since then I have dissected and examined twenty additional amputated lower extremities, making twenty-eight[1] in all, and have carefully followed the clinical course of more than fifty patients. In a paper which appeared in this JOURNAL,[2] as well as in two succeeding contributions, one on the condition of the veins,[3] and the other on the symptom complex presented by associated migrating phlebitis of superficial veins,[4] it was definitely stated that a distinct clinical and pathological entity, *thrombo-angiitis obliterans*, was under consideration. In the same issue of this JOURNAL,[5] Sachs, writing on "Raynaud's Disease, Erythromelalgia and the Allied Conditions, and Their Relation to Vascular Disease of the Extremities," expressed views which are completely divergent from my own, with the result that a great deal of confusion has arisen in regard to what thrombo-angiitis obliterans really is, and as to how it is related to Raynaud's disease and erythromelalgia. Having received a number of inquiries on this topic of late, I wish to state my own view briefly here.

Thrombo-angiitis obliterans is in no way related to either Raynaud's disease or erythromelalgia. Patients suffering from thrombo-angiitis obliterans, however, may present a clinical picture which has been and is sometimes diagnosticated as one or the other of the two latter conditions.

The following statement is found in Sachs' paper: "According to Dr. Buerger's studies the morbid changes are the same whether the case be designated clinically as erythromelalgia, Raynaud's disease, or acrocyanosis." This is a rather unfortunate misunderstanding. My own clinical observations lead me to the opinion that the designations erythromelalgia and Raynaud's disease are not applicable to the usual clinical pictures characteristic of thrombo-angiitis obliterans. It is the redness in the dependent position, a striking symptom of thrombo-angiitis obliterans, and the pain that may lead the clini-

[1] These will be reported in detail by the author and Miss Adele Oppenheimer.
[2] AMER. JOUR. MED. SCI., 1908, cxxxvi, 567.
[3] Jour. Amer. Med. Assoc., 1909, pp. 1319 to 1325.
[4] International Clinics, vol. xiii, 19th series, pp. 85 to 106.
[5] AMER. JOUR. MED. SCI., 1908, cxxxvi, 560.

cian to think of erythromelalgia, and the gangrenous termination which may cause confusion with Raynaud's disease. I would digress too far from my theme were I to adduce all the evidence I possess in favor of the assumption that the red blush is but an expression of the attempt to compensate for impoverished circulation by virtue of dilatation of superficial capillaries. It is a phenomenon found also in certain cases of arteriosclerosis or diabetic gangrene, although less striking in these latter conditions.

Some ten years ago Sachs and Wiener, in papers on erythromelalgia,[6] endeavored to show by the pathological findings in a case that the lesion in erythromelalgia is an obliterating process of the arteries. Cassirer, in his monograph[7] on Vasomotor and Trophic Neuroses, expresses the view that they were dealing with a case of "endarteritis obliterans," or, as I term it, "thrombo-angiitis obliterans." This, too, is my conviction.

Of late I have been able to prove by the clinical and anatomical study of two cases[8] that belong to the group of "acrocyanoses,"[9] that gangrene can occur without organic arterial change. This is in all probability also true for Raynaud's disease.

Thrombo-angiitis obliterans is a clinical and pathological entity characterized by thrombotic occlusion of arteries alone or of arteries and veins, giving subjective manifestations, chief among which are pain and the peculiar symptoms of intermittent claudication, and presenting objective phenomena, the most important of which are redness in the dependent position of the limb, marked blanching in the elevated position, evidences of arterial occlusion in the form of pulseless vessels, trophic disturbances of moderate extent and of even grave consequence often terminating in gangrene of one or both lower extremities. We possess no data which tend to show that either erythromelalgia or Raynaud's disease is dependent upon organic obliteration of arteries or veins. Clinically, thrombo-angiitis obliterans may show many variations from a set form, and this accounts for the fact that the true condition is so frequently overlooked. Associated migrating phlebitis and symptoms of intermittent claudication are but two of a number of phases that may stand out as striking features. Individual characteristic symptoms of thrombo-angiitis obliterans do not justify us in establishing a relationship between this disease and others in which somewhat similar phenomena may be found.

[6] Mount Sinai Hospital Reports, 1898, and Phila. Med. Jour., June 29, 1901.
[7] Vasomotorisch-trophischen Neurosen, Berlin, 1901, pp. 145, 163, 164, 193.
[8] To be published with Miss Adele Oppenheimer.
[9] They could be regarded as atypical cases of Raynaud's disease.

FOUR CASES OF CERVICAL RIB, TWO OF THEM FLAIL-LIKE.

By A. P. Francine, A.M., M.D.,

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Three of the following cases occurred at the State Dispensary for Tuberculosis (No. 21), one in the service of Dr. John C. Da Costa, Jr., one in that of Dr. Samuel A. Munford, and one in my own. The fourth case was kindly added by Dr. John Speese from the Surgical Dispensary of the University Hospital. I am indebted to Dr. Alfred Stengel for the interesting skiagram of a case in which cervical rib was suspected clinically, but which the *x*-rays showed to be the elongated transverse process of the first thoracic vertebra.

It is not my purpose to review the literature of cervical rib nor to discuss the classification, diagnosis, symptoms, or treatment, as this has all been done by others, notably by Keen.[1] The usual types of cervical rib are relatively so frequently discovered today as to be unworthy of detailed report on account of any rarity of the condition or of any special clinical interest pertaining to it. But it seems not out of place to put on record two of the following cases, showing, as they do, a curious and uncommon anomaly, namely, a cervical rib with a distinct joint or articulation in its continuity, being flail-like and having two sections.

So far as I have been able to observe, the diagnosis of cervical rib, certainly in the great majority of instances, and even in the absence of symptoms to call attention to the condition, presents no difficulties (though it should always be confirmed by the *x*-rays). It would be much more frequently detected were careful clinical methods more generally followed in routine dispensary work. This has been particularly suggested by the discovery of the three cases in the State dispensary service within a relatively short time, especially as each of the patients had been previously treated at several other hospitals and belonged to what might be termed the indigent itinerant sick.

Case I.—L. D. (State Dispensary, Case No. 880, service of Dr. Francine), a white female, aged twenty-nine years; married; a Russian Jewess; five children. There is no family history of tuberculosis and no history of contact with it. The stated illness began two months previously with some blood spitting and cough, a few night sweats, and loss of weight. The highest weight in health was 135 pounds; the present weight is 122 pounds. Height, five feet

[1] Amer. Jour. Med. Sci., 1907, cxxxiii, 173.

two inches. Temperature A.M., 99.2°; pulse, 84; respirations, 20. The pulmonary lesion is an active infiltration of the right apex moderately advanced.

The patient says that for the last two years she has had occasional mild pains in the left shoulder with an occasional "pricking" sensation in the left forearm; she has no pain at present.

Physical examination reveals a small mass in the cervical end of the supraclavicular fossa about an inch above the clavicle, which might readily be mistaken for an enlarged gland, except that it is of bony hardness and immovable, and upon deep palpation may be traced back to the cervical spine. There is no general tenderness, but firm pressure upon the mass gives slight pain. Upon the right side a similar and smaller mass may be palpated, with less distinctness. The skin of the shoulders and arms is normal. There is no pulsation or other signs.

Dr. Henry K. Pancoast, the röntgenologist to the Hospital of the University of Pennsylvania, has kindly described the radiogram (Figs. 1 and 2) as follows:

CASE I.—*Right Side.* There is a rudimentary cervical rib about one inch long and tapering to a pointed free extremity. The head is ill-defined and probably not well developed. The neck is obscured by the shadow of the transverse process. There is a very close articulation with the transverse process of the seventh cervical vertebra. A joint line can just barely be determined, and a thickened portion of bone indicates the tubercle of the rib. At a first glance, however, the appearance is almost that of an abnormally developed transverse process rather than of a rib. The *first rib* on this side articulates with the first dorsal body only, and not with the lower edge of the seventh cervical in addition, as is almost always the case when a cervical rib is present.

Left Side. The following interpretation of the appearance of the cervical rib on this side is offered after a careful study of the radiogram. There is a poorly defined and not well-developed head articulating with the seventh cervical body. The neck is short and slender. A well-developed tubercle articulates with the transverse process of the seventh cervical vertebra. This articulation is structurally well developed and is clearly defined. The body of the rib appears to be approximately about one and one-half inches long, and terminates in a slightly broadened and distinct articular surface. With the latter a second body seems to articulate. There is a well-defined appearance of a joint. There is sufficient space between the articulating ends to suggest the presence of articular cartilage. This second body is about the same length as the proximal one. The head of the *first rib* on this side seems just barely to touch the lower margin of the seventh cervical body, being a little higher than the head of the first rib on the opposite side.

This unusual radiographic appearance has not previously been

observed by me either in the dozen or more cases examined personally or in radiograms made by others. Neither were any reports of such a type of cervical rib found when making a partial review

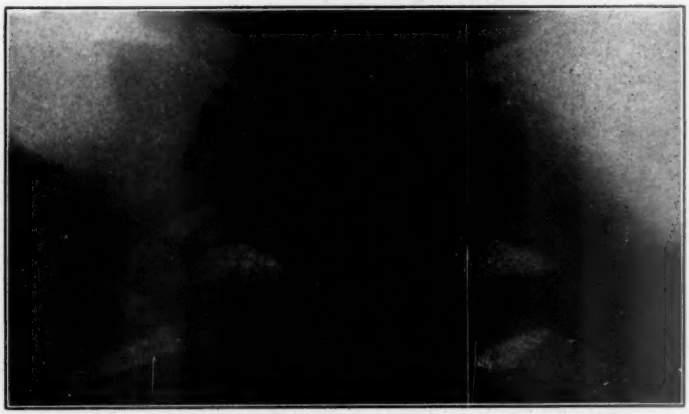

FIG. 1.—Bilateral cervical rib (Case I). Note the flail-like rib on the left, with a distinct articulation or joint in its continuity.

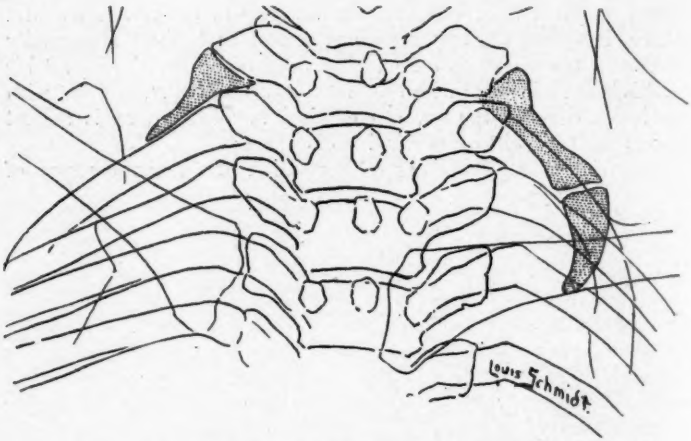

FIG. 2.—Tracing of the skiagram shown in Fig. 1

of the literature on the subject, in 1902. A lack of knowledge concerning more recent literature renders any conception as to the frequency of occurrence of this unusual form impossible.

CASE II.—L. M. (State Dispensary, Case No. 1409, service of Dr. J. C. Da Costa, Jr.), a white male, aged thirty-three years, married; native of the United States. One child. No family history of tuberculosis and no history of contact. The stated illness began four months previously with cough and expectoration, some hoarseness, and loss of weight. Some blood spitting occurred in the last month. The highest weight in health was 158 pounds, the present weight is 136½ pounds. Height, five feet seven and one-half inches. Temperature A.M., 98.4°; pulse, 94; respirations, 24. The pulmonary lesion is an infiltration of the right apex, moderately advanced.

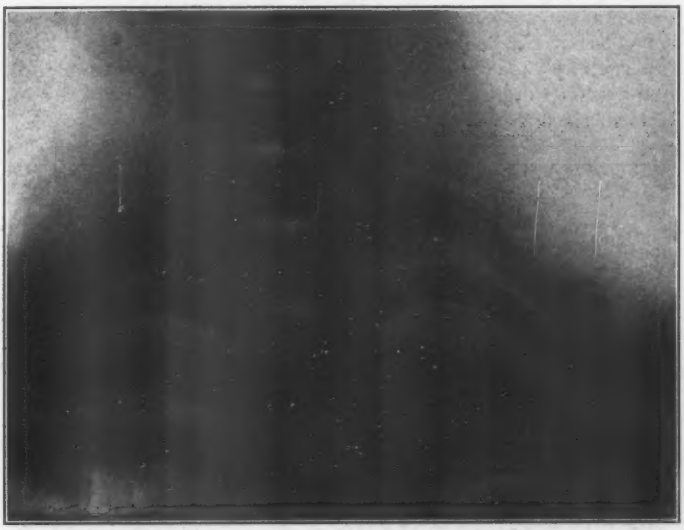

FIG. 3.—Bilateral cervical rib (Case II). Note the flail-like rib on the left, with a distinct articulation or joint in its continuity.

He complains of some pain in the left shoulder; at times this is sharp; no tenderness.

Physical Examination. One and a quarter inches above the left clavicle and toward the cervical end of the supraclavicular fossa a small, hard, nodular mass is felt, extending backward toward the cervical spine. Deep palpation in the right supraclavicular fossa reveals a corresponding, though much smaller, nodule. The shoulder and arms are otherwise normal.

The following interpretation of the radiogram (Fig. 3), made by Dr. Menges, of the Jefferson Medical College Hospital, is based upon a comparative study of the radiograms of both cases:

Right Side. A complete rib articulating at its origin with the body and transverse process of the seventh cervical vertebra. The

body terminates in front probably in a common cartilage with the first rib, the inner end of which is lower than on the left side, as is usually the case. The *first rib* on this side articulates as it would normally, just as in the first case, with the first dorsal body only, and not with the body of the vertebra above in addition.

Left Side. A well-formed but more slender rib. The head is poorly developed, the neck narrow, and the tubercle small, as compared with the same portions of its fellow of the opposite side. At a point corresponding to about the middle of a complete rib, it terminates in a broadened and distinct articular surface. It here articulates apparently with a second bone about one and one-half to one and three-quarters inches in length. The latter tapers to a point, but terminates rather indefinitely, being obscured by the superimposed shadows of the first rib and spine of the scapula. Its termination would seem most likely, however, to be like that of a cervical rib of the third degree in development.

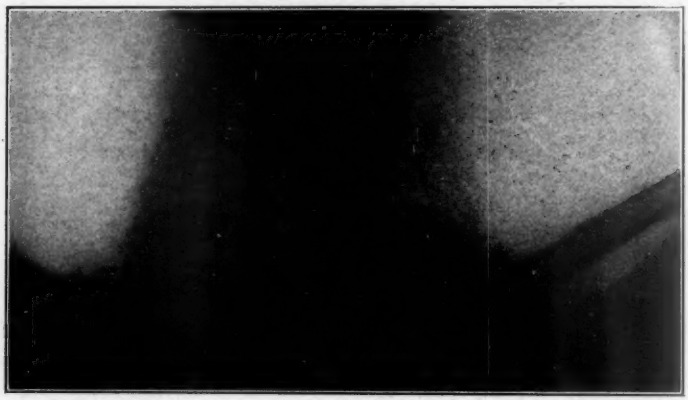

FIG. 4.—Radiogram of a case which clinically suggested a cervical rib. The real condition was an elongated transverse process of the first thoracic vertebra with great obliquity of the first rib. (To be compared with Figs. 1 and 3.)

The *first rib* on this side articulates with the body of the first dorsal and lower margin of the body of the seventh cervical vertebra, as is usually the case when cervical ribs are present. It has a longer neck than its fellow of the opposite side, and the transverse process of the first dorsal vertebra is longer on this side than on the right.

CASE III.—J. T. (State Dispensary, Case No. 1387, service of Dr. S. A. Munford), a white male, aged twenty-five years, presented himself at the State Dispensary for Tuberculosis for an examination as to the condition of his lungs. The past history was not of special importance. The individual was tall and gaunt, with the typical thorax of advanced pulmonary tuberculosis. In

the right superclavicular fossa was a tumor, while the superficial veins from the right arm were distended. Palpation proved the tumor to be somewhat yielding and hard, with a large artery lying upon it. The left fossa contained a somewhat similar tumor distinctly palpable, though not visible. There were no symptoms, nor had there been any. In answer to questions, he stated that his attention had been called to the mass once previously, that being the first intimation of its presence.

The two objects were thought to be cervical ribs, and this diagnosis was confirmed by two skiagrams, one taken by Dr. Menges, and one by Dr. C. L. Leonard. They reveal a double cervical rib, each about three inches long, with well-developed head, neck, and tubercle. Both articulate with the seventh cervical vertebra. The first rib on the right side articulates with the lower margin of the seventh cervical, while the one on the left does not.

Case IV.—Patient of Dr. John Speese. An unmarried woman, aged twenty-three years, was admitted to the Surgical Dispensary of the University Hospital, complaining of pain, numbness, and tingling of the right arm and forearm. The symptoms began one year previously, and had gradually grown worse, and were accompanied with loss of muscular power and cyanosis of the arm. She was unable to account for this condition, and there was nothing in her past history which was suggestive. Examination of the right arm showed decided weakness of the muscles, but no atrophy. The arm was cold on palpation, and the right radial swollen and weaker than the left, but the two beats were synchronous. The axilla was negative. In the cervical region, directly beneath the sternocleidomastoid and making this muscle rather prominent, a hard mass was palpable. The mass was immovable and felt like a portion of rib. The diagnosis of cervical rib was made, confirmed by *x*-rays, and operation recommended. The patient refused operative interference and did not revisit the dispensary. There were no symptoms produced on the left side. The *x*-rays showed bilateral cervical ribs.

The skiagram was taken by Dr. H. K. Pancoast, who reports as follows:

Right Side. An incomplete rib about two and one-half inches long by radiographic measurement, with well-developed head, neck, and tubercle. It articulates with the seventh cervical vertebra. The body is unusually stout, being thicker than the posterior portion of the first rib, and terminates abruptly in a somewhat expanded extremity, presenting an appearance which was at first mistaken for an articular end. The head of the first rib on this side seems barely to touch the lower margin of the body of the seventh cervical vertebra.

Left Side. Incomplete rib of about the same length, articulating with the seventh vertebra. The head is not so well developed

as on the other side, and the neck is longer and more slender, corresponding to the greater relative length of the transverse process of this vertebra on this side. The tubercle is likewise not so well developed. The body is more slender and tapers down to a pointed extremity, unlike its fellow. The first rib does not seem to be in relation with the body of the seventh cervical vertebra on this side, its articulation being lower than on the right.

As Cases III and IV conform to the usual type of cervical rib, it was considered unnecessary to reproduce the skiagrams in the text.

Keen, presumably referring to this flail-like condition of a cervical rib, says: "In several cases a joint has been noticed some distance from the first rib, in which case the specimen might be described as a cervical rib articulating with a longer or shorter exostosis. Not uncommonly, this projection from the first rib, which, so to speak, rises up to a greater or less extent to meet the rib, is apt to be thickened at the point of junction and produces a tumor consisting of two portions nearly at right angles to each other."[2]

From a careful study of the skiagrams in Cases I and II herewith reported, I feel that the second portion of the cervical rib is not an exostosis from the first rib, but a true phalanx or distal segment of the cervical rib itself.

I think this is the more likely explanation on theoretical and anatomical grounds, for while the tip of this portion is not distinctly visible in the skiagrams, being merged in the shadow of the first rib and spine of the scapula, yet there is the absence in this position of any dense shadow, as would likely be the case if it were an exostosis and formed a base. The slender, tapering character of this bone, its small end being in juxtaposition with the first rib, and the angle it assumes in relation to the first rib, taking a direction upward and inward, also tend to confirm my view.

[2] See Weissenstein, Ehrich (Madelung), Quervain, Ranzi, Adams, Avon, Tillmanns, and Borchardt.

REVIEWS.

EXERCISE IN EDUCATION AND MEDICINE. By R. TAIT MCKENZIE, A.B., M.D., Professor of Physical Education and Director of the Department, University of Pennsylvania. Pp. 406; 346 illustrations. Philadelphia and London: W. B. Saunders Co., 1909.

EXERCISE has for many years been dealt with by authors more or less qualified to write about it from different standpoints. A half-century ago Taylor wrote on the *Movement Cure*, with special reference to the system of Swedish gymnastics. Forty years ago Maclaren's *Physical Education*—although two-thirds of it was a mere description of the use of gymnasium apparatus, and resembled a Spalding catalogue—was greeted as epoch-making. Thirty years ago Blaikie's *How to Get Strong* (in spite of the execrable English of its title) had a considerable vogue. Twenty years ago a translation of Angerstein's *Home Gymnastics for the Sick and the Well* —largely another list of movements and contortions supposed to accomplish remarkable results—was widely consulted. About this time White recorded his opinions under the title, *A Physician's View of Exercise and Athletics*, and many other magazine articles dealing with various aspects of the subject have since been published. Sargent's *Health, Strength, and Power* (1904) was a book of some merit, but was disappointingly elementary and much overloaded with illustrations of special exercises. During this time very valuable treatises on artistic anatomy—the best of which was Arthur Thomson's—and very valueless essays on *The Culture of Beauty* have been published. So far as we know, however, no single book in English has covered this entire field in a manner that is at all comparable with Professor McKenzie's treatise, either for scientific accuracy, literary skill in the presentation of the subject, or comprehensive consideration of all the collateral and allied topics. It has—as the title indicates—two main subdivisions, *Exercise in Education* and *Exercise in Medicine.*

In Part I the author has tried to interest and instruct the individual—layman or physician—who is interested in exercise, whether as to his own habits or in relation to schools and playgrounds, and who, in either case, desires to have some guide in reaching a conclusion. In Part II the application of exercises to pathological conditions is taken up, and, for example, flat-foot, round shoulders,

scoliosis, circulatory and nervous diseases, obesity, locomotor ataxia, and nutritive disorders are dealt with.

There is much to praise and selection is not easy, but some of the more striking features of the book may be noted.

The differentiation of exercises into those of endurance and those of effort is discussed fully, and the overlapping of these classes is clearly defined. For the first time in a book on exercise the physiological condition, as indicated by facial expression, is shown and is illustrated by original masks, confirmed by instantaneous photographs. The physiological chemistry of muscle is set forth and original observations with the Stanton machine on blood pressure are recorded; there is a full discussion of the variations in blood pressure in exercises of effort and endurance; the relation of the nervous system to exercises of skill, strength, and endurance is explained. The effects of elimination are shown by observations on football players at Pennsylvania, and also by tracings from Lombard's balance, published for the first time. There is a new classification of gymnastic apparatus given, and the German and Swedish systems of exercise are described.

The various "systemettes" are summarized. The Japanese "Jiu Jitsu" is illustrated from original sources that have not hitherto been generally available. The article is the most dispassionate and comprehensive review of the merits and demerits of this system that is to be found in English.

One chapter covers the period of growth from infancy to maturity, and contains valuable original classifications of games, exercises, and gymnastic apparatus; it ends with a concise prescription of exercise for sedentary men of middle age. Another gives those facts connected with the construction and management of playgrounds that should be familiar to every physician, teacher, or member of any city or town council who wishes to know accurately how playgrounds should be established, equipped, or conducted. It is illustrated by plans and photographs of playgrounds in operation. The exact amount and the nature of the exercises that should form part of the day's course for school children, from the kindergarten to the high school, including school-yard games, are set forth in a clear and interesting manner.

There is a short historical sketch of physical education in the early American colleges, with a full description of the department of physical education at Pennsylvania, and with illustrations of the forms used, of classes at work indoors and outdoors, and an outline of a typical year's course. This is followed by a discussion of the ideal physique of the college student, illustrated by Dr. McKenzie's statuette, the "Athlete," and by a complete set of original photographs of classes at work.

The physical education of the blind and deaf-mute is for the first time carefully described.

The treatment of mental defectives in schools and institutions—showing the best exercises and the possibilities for improvement in different grades—is summarized in an original and practical way, and for the first time. This concludes Part I, which has thus covered the physical education of the normal and the slightly defective individual from infancy to maturity, and has dealt with various minor subjects.

Part II opens with a general chapter on the application of exercise to pathological conditions, describing, for example, the use of massage in sprains, the place of exercise in the treatment of pulmonary tuberculosis, and the value of deep breathing in the prevention and cure of disease. Original drawings and photographs of the anatomy of the foot, and of its mechanics, are given in connection with the treatment of flat-foot. Round-back, stoop-shoulders, and scoliosis are discussed, and the movements and musculature of the spine and thorax are described in this connection most completely and thoroughly. Numerous tracings taken from Dr. McKenzie's cases illustrate the various forms of curves. The treatment by exercise and the prognosis in functional and in osseous curves are judicially discussed. Typical prescriptions for the three most common forms of curvature are given, and are illustrated by original photographs and reports of cases.

The whole question of exercise and athletics as a factor in the production of disorders of the circulation is reviewed, the general conclusion being that athletes are slightly longer-lived than non-athletic students. The relation of athletics to arteriosclerosis remains undetermined, but there does not seem to be any definite evidence that they hasten its onset. Oertel's treatment and the Schott treatment are fully considered, and there are original illustrations of each movement, and of the movements suggested by Satterthwaite. The role of exercise in cases of obesity (in addition to diet, and the use of thyroid extract) is covered, and there are well illustrated prescriptions of exercises and an outline of the way in which they should be modified. Gout, diabetes, and rheumatism are also discussed in a general but very satisfactory manner. The treatment of constipation by massage, by vibration, and by duplicate and active movements is thoroughly described. The section on hernia is new and somewhat radical, but is most interesting. The final chapter is devoted to the treatment of the nervous system. This has not been so fully considered in any book on exercise that we have seen.

The book as a whole is not only the most thorough and satisfactory yet written on the subject, but it is the most modern and scientific. It may readily be understood by the layman, yet is replete with information valuable to the professional man, but not usually in his possession. It is, moreover, interesting throughout, and can be read for pleasure as well as for profit. J. W. W.

THE PROBLEM OF AGE, GROWTH, AND DEATH. By CHARLES S. MINOT, Professor of Comparative Anatomy, Harvard Medical School. Pp. 280; 73 illustrations. New York and London: G. P. Putnam's Sons, 1908.

IN this book Dr. Minot has collected the views which from time to time he has expressed in various papers and addresses, upon the subjects included in the title, the volume being cast in the form of a series of public lectures delivered before the Lowell Institute and illustrated by reproductions of lantern slides used at the time of presentation.

After outlining the characteristics of senility the author points out that the structural evidences of senescence of cells consist in the assumption of structural and physiological differentiation, in cytomorphosis; that with a few exceptions this consists, from a morphological standpoint, in the decrease in nuclear material in the cells and in the growth of the protoplasm; and that the evidence of the youth of cells is the converse of these characters, the increased proportion of nuclear matter and the small amount of protoplasm. With this basis and with the realization that with differentiation cells lose their power of active multiplication possessed as an eminent character in their youth, he points out that senescence, the process of differentiation and maturing, finds its greatest rate of development in the earliest periods of existence of the complex organism, highest in the earliest embryonic periods, and rapidly lost through later embryonic life to the extent that the rate of growth at the time of birth is but a small percentage of what it was in the early proliferations occurring at this period, and in postnatal life quickly descends to an almost level minimum in earliest childhood. This rate of growth he estimates by weight comparisons, and correlates it with evidence of cell proliferation (mitotic index) in the tissues, recognizing that body growth is the result rather of cell multiplication than of increase of cellular size. In other words, paradoxical though it seem, we grow old most rapidly in the antenatal and earliest postnatal life, and progressively less and less rapidly as temporal age advances. Rejuvescence, manifested in a limited sense in regenerative processes and repair of waste in nature, finds its highest and most satisfactory manifestations after sexual fertilization of the female germ cell in the inception of the fresh generation; and the utility problem narrows down to that of slowing cellular senescence after maturation and before actual senility (for senility in the stages of cytomorphosis is not only a progressive differentiation, but in addition degeneration which is followed by death of the cell and its removal). This problem has no immediate answer, but to the mind of the author is not unpromising of some solution. This phase of the matter receives less consideration than one might hope, although the author undoubtedly escapes much that may be rash in prognosti-

cation. It surely must lie, at least in part, in attempting to adjust the organism so as to escape the omnipresent but adventitious causes of wear and tear from excess of function, of infection, and of accident. Whether with such influences eliminated there be a possibility of further slowing the rate of senescence into actual senility and to natural death is the more precise point which the author believes is perhaps possible, but which he acknowledges as at present unanswerable in satisfactory manner. The fact that thermic and chemical conditions have been shown to influence cellular growth, multiplication, and differentiation affords reason for suspecting that there may be in the future some return to the inquiry.

Natural death does not follow in the same train in the complex and the simple monocellular organism. In the former at the time of birth the vast bulk of the component cells are free from changes necessitating their demise, they die because of the loss of some important group whose existence and functional ability are essential to the harmonious life of the whole body group. In the monocellular organism, however, natural death depends upon the wearing out of the single cell. The author doubts (and it would seem very properly in the light of the numerous examples which within the past decade have been established of sexual reproduction following an asexual cycle in protozoa) whether the older idea of the essential continuity of matter and virtual immortality of monocellular organisms should be accepted. They probably follow the same lines as seen in higher organisms, rejuvescence by conjugation or definite sexual fertilization, senescence progressing through a series of asexually reproduced organisms until the later members of the cycle are so deteriorated that they become unviable or are restored by a second fertilization. So in this sense is there a continuity of the germ plasm of the higher organisms, through an isolated group of germ cells developing into the sexual cells with the differentiable body cells developing in each generation from this continuous stem.

The author does not in the general text advert to the real nature of life; but is entirely frank in that in one of his appendices (page 272) he deliberately states his belief that no theory of life so well harmonizes with its recognized manifestations as one which includes the existence of a mysterious and as yet untouched vital force working through the multimorphic and multikinetic protoplasm as a physical basis.

The book is well adapted for the laity as well as for scientific readers, its simplicity of style and the many presentations of the personality of the author in familiar relation giving it no little charm. The matter is not so much the presentation of new as the novel presentation of that which has been known, but not applied in quite the manner and for the purpose of the present author. That the rate of growth is greatest in the earliest periods has long been appreciated; Cohnheim, for instance, used this fact as a sustaining argu-

ment for the verity of his theory of tumor formation, claiming that thus tumors, which spring from "cell residua," representing early embryonic periods, must grow much more rapidly than those coming from rests developing later. Richness in nuclear matter, small proportion of protoplasm, absence or incompeteness of differentiation have long been regarded as evidence of the youthful type of cells and the converse of mature cells. But the particular adaptation to show that age progresses most rapidly in the earliest, and more slowly in the more advanced periods of life, is new and of interest and significance. It has its more immediate bearing upon the broad biological conception of life and living things, but may well find eventual application, even though at present from the utilitarian standpoint it seems no more than collateral evidence of the reasonableness of efforts to prolong life to a natural death at a later period than is ordinarily seen in human beings. It would be no matter of advantage to intelligent beings that differentiation should be slowed in the period of extreme youth, even could such a result be effected; the senescence of differentiation of structure and function must be accepted for the acquirement of that grade of intelligence and other functions which make life worth the living, even though the price of the acquisition be inevitable death. In the slowing of the post maturation stage rests the real problem, not necessarily involving the entire mass of component cells of the system, but at least those groups essential to bodily persistence and performance of functions essential to the individual. Whatever the answer, it cannot evade death; rejuvescence of the individual is impossible, it can merely look to the prolongation of the mature period of life; much aging must necessarily have already been experienced, and it can only lie (adventitious causes of disease and death being disregarded) in more perfect maintenance of functional harmony in the body, in the avoidance of partial and general functional exceses and (what is in reality the same thing) in adjusting by will or by environment the rate of living to the simplest needs.

A. J. S.

PROTOZOÖLOGY. By CARY N. CALKINS, Professor of Protozoölogy in Columbia University, New York. Pp. 349; 125 illustrations; 4 colored plates. New York and Philadelphia: Lea & Febiger, 1909.

WHATEVER the ultimate quantitative limit of the field of protozoölogy in medicine, there can be no doubt that it must be accorded the qualitative dignity of bacteriology as a branch of study dealing with the causation of disease. That it should at present be less developed than bacteriology, of course, can easily be under-

stood when we realize that the cultural methods employed in the latter subject are only in the most limited measure applicable to the protozoa. Moreover, it is doubtful whether we will ever be able to systematize as satisfactory methods for the extracorporeal cultivation of these organisms, owing to the fact that the life history of each is made up of stages more or less distinct from one another and that the conditions for each, in some measure, vary. Further, there is reason for us to believe that even where cultivation is possible, cultural variations of such marked type are likely to arise that it will only be after extensive study that one can establish the identity of the organism in each of such variations. For these reasons protozoölogy must necessarily, to a much greater degree than bacteriology, depend upon morphological studies. This must mean that the investigator must acquire familiarity with a wide range of minute organisms, and each in a number of different appearances; and further, that investigations must, to a very great extent, depend upon the most painstaking microscopic examination of each part of the material under investigation. Time and long preliminary preparation must be demanded of the protozoölogist, and it can scarcely be expected that the ordinary practitioner of medicine will ever be in a position to devote himself, save in a very superficial manner, to such a study. It is possible that such methods of cultivation as have been accomplished by Novy in the case of trypanosomes, or of Musgrave in the case of the amœbæ, may be extended to facilitate the work; but little can be hoped to obviate the very much greater amount of direct individual attention to morphological characteristics of the material on the part of the trained laboratory worker than is required in bacteriology.

Dr. Calkins' book is an evidence of the growing interest which the medical profession holds toward the protozoa, and the fact that it is written by a protozoölogist rather than by a medical man indicates the difficulties which would be encountered by the latter in the study of these intricate life histories. While Dr. Calkins inveighs against the restriction of protozoölogy to pathogenic forms, and urges upon the profession the very great value of the study of the protozoa in the appreciation of the various vital processes, both normal and pathological, yet the reader will not be disappointed in his expectation of finding that the work deals largely with the pathogenic forms.

The book is based upon a series of lectures before the Lowell Institute in 1907. The first portion (which closely recalls the author's former book on *The Protozoa*) is devoted to a systematic discussion of the general organization of protozoa, their physiological activities, and the phenomena of their life cycle, a separate chapter being given up to conjugation, maturation, and fertilization. An extremely important chapter is devoted to parasitic relations of the protozoa, the lives of these organisms as parasites, the modes

of transmission, the exogenous life of protozoan parasites, and reference to the effects of protozoan parasites upon their hosts. The latter chapters of the book are given over to consideration of pathogenic varieties. Under the flagellates, the spirochetes and their position in nature are fully discussed; and various problems that have arisen in connection with the amœba and dysentery, the nigri bodies in rabies, Guarnieri's bodies and smallpox, as well as obscure diseases subject to protozoan origin, are fully discussed.

Dr. Calkins' reputation as a protozoölogist and the close and much appreciated interest which he has taken in medical problems in which protozoölogy has application are a guaranty of sympathetic and full consideration of such questions. The work undoubtedly is a forerunner of other books upon the same subject, and will itself be the basis of studies in our medical laboratories in protozoölogy. It is admirably adapted as a text-book in schools where it is contemplated this branch may be taken up as part of the course of instruction; and while it does not pretend to include all forms of known pathogenic protozoa, and therefore cannot be regarded as a systematic treatise, it is an absolutely essential volume in the laboratory of every worker in clinical or general pathology or in any branch of etiology. A. J. S.

THE PRINCIPLES AND PRACTICE OF PHYSICAL DIAGNOSIS. By JOHN C. DA COSTA, JR., M.D., Associate in Clinical Medicine in the Jefferson Medical College; Chief of the Medical Clinic and Assistant Visiting Physician to the Jefferson Hospital, Philadelphia. Pp. 548; 212 illustrations. Philadelphia and London: W. B. Saunders Company, 1908.

DR. DA COSTA has prepared a very excellent work on physical diagnosis, of which forty-five pages are devoted to the general methods, four hundred to the thorax, and sixty-four to the abdomen. The book is distinctly readable. The descriptions are, as a rule, clear, sufficiently detailed, and written evidently by one who possesses not merely a book knowledge of the subject, but who has tested for himself and reached definite conclusions upon the majority of the methods that he describes. Each section is introduced with a brief paragraph upon the clinical anatomy, and each disease described is preceded by a paragraph upon the clinical pathology. The latter paragraphs constitute a valuable addition to the book, and at any rate for the student, serve to make more understandable the physical signs that are subsequently described.

It is not to be supposed, however, that Dr. Da Costa is greatly superior to his predecessors in overcoming some of the inherent diffi-

culties of the subject. His discussion of the quality of percussion sounds is practically a statement that sounds have different qualities. In his discussion of pitch, he regards the sound elicited by percussion apparently as a single note and not, as it really is, a complex of vibrations of different rates.

The section on the examination of the thorax is enriched with many satisfactory illustrations that, without repetition, serve to emphasize the points brought forth in the text. As in other works of this character, the nude human female serves as a model upon which to sketch the various outlines and symbols that are supposed to elucidate the description of the physical signs. This seems to us an unnecessary subordination of science to assumed art. Aside from this the diagrams and illustrations and, in particular, the sphygmocardiograms are of unusual excellence. The signs to which proper names are attached are given quite fully, but it would be of advantage if references to the original article or work were appended. Dr. Da Costa has evidently preferred not to quote literature, although he is undoubtedly familiar with it, and in this manner has probably lessened the bulk of his book, but even for students, we think, some references are desirable.

There are a few points to which we should like to call attention. He fails to mention the fact that a normal percussion resonance may occasionally be obtained over a pneumothorax cavity. The diagrams of the respiratory and cardiac sounds add little if anything to the description from the text. It should be noted that œgophony may be heard over as well as above a pleural effusion. The paragraph on the physical signs of bronchiectasis is inadequate, and is misleading in so far that the dilatation of the small bronchi, which is the commonest pathological condition of this nature, does not give rise at any time to the signs of cavity. In regard to the movable dulness of the pleural effusion, it is stated that it is rarely demonstrable as a result of change in posture of the patient. This is surely not the common experience. Kussmaul's pulsus paradoxus has not in our experience been frequently demonstrated in obliterative pericarditis, and Friedreich's diastolic collapse of the jugulars is an equally elusive sign. Dr. Da Costa is one of the few writers who calls attention to the enfeeblement of the second sound at the base as significant of myocarditis. He speaks too confidently of the existence of relative pulmonary regurgitation.

The section on the examination of the abdomen and the abdominal viscera is entirely inadequate. The illustration of enteroptosis is rather an exaggerated than a usual form of this condition. The description of the examination of the intestines is very brief and auscultation is dismissed with a disparaging paragraph.

Much could be said in praise of the different parts of this book were it not for the restricted space at our disposal. J. S.

TUBERCULOSIS: A PREVENTABLE AND CURABLE DISEASE. By S. ADOLPHUS KNOPF, M.D., Professor of Phthisiotherapy in the New York Post-graduate Medical School and Hospital. Pp. 394; 115 illustrations. New York: Moffat, Yard & Co., 1909.

THIS book, dedicated alike "to the Masters of Medicine, to the Noble Men and Women, and to the Statesmen and Philanthropists who strive for the eradication of the Great White Plague," can be appreciated by those in all walks of life. To the consumptive himself it is offered, not to replace the services of the physician, but to show him how to live. To all, the author trusts that the volume may lend assistance.

Clearly and comprehensively the book stands out as one of the best which has appeared upon the subject. Chapters I, II, and III are devoted to the duties of the patient, people, and physician, respectively. In chapter IV suggestions are made so that the patient may receive sanatorium treatment at home. The remaining chapters point out the duties of employers, school teachers, the clergy, charity organizations, etc. A brief description of the various state sanatoria is included. Emphasis is laid upon the value of the "preventorium" as well as the sanatorium. Municipal measures, which have been instituted for the establishment of out-of-door schools, day camps, dispensaries, etc. are described. No phase of the subject is omitted. Numerous photographs lend attractiveness to the book and these are well described in the text. The author not only graphically describes the subject in hand, but many suggestions of betterment are made, among these being the solicitation of the government in providing adequate disinfection of mail bags. The book forcibly reflects the great enthusiasm of its author. Though the diction is generally simple and appreciable to the lay mind, now and again "scientific digressions" occur—pardonable, in view of his enthusiasm. Attractiveness of style and thoroughness of compilation are features. W. T. C.

THE HISTORY OF THE STUDY OF MEDICINE IN THE BRITISH ISLES. By NORMAN MOORE, M.D. (Cantab.), Fellow of the Royal College of Physicians, Physician to St. Bartholomew's Hospital, London. Oxford: At the Clarendon Press, 1908.

THESE four lectures are very fascinating for one who is interested in the history of the development of medical science. The author evidences a vast store of erudition upon which he draws, and he presents it in such an attractive manner that the reader is carried along with interest and pleasure. The first lecture treats especially of Dr. John Mirfeld, in whose person was exemplified what old Cotton Mather termed "the angelical conjunction of physic and

divinity." Along with his account of this fourteenth century physician, Dr. Moore offers us a brilliant picture of the state of medical knowledge and the conditions of medical study in the England of that period. The second lecture describes the education of physicians in the seventeenth century in London, dealing especially with that of Edward Browne. The author shows how in this century dissection and observation supplanted the reading and studying of the ancients, which had constituted the education of physicians during the previous centuries. In the latter part of the seventeenth century, dating from the period of the Restoration in England, men of intellect turned with vigor to the study of natural phenomena. As J. R. Green says, they were wearied with the subtleties of religious disputation, and the reaction against Puritanism extended not only into their moral life, but led to an intellectual reaction which was fully as important, if not more so. It was at this time that the Royal Society was founded. We are all familiar with the galaxy of distinguished names including those of Newton, Locke, Boyle, and Flamsteed, in addition to the eminent physicians, Sir Theodore Mayerne, Harvey, and Sydenham, who were among its earliest and most famous members. Of course, it is to the members of the medical profession that Dr. Moore directs particular attention, but the passion for medical research which arose at this time can only be correctly studied as a part of the great scientific spirit which then permeated the nation. In the third lecture Dr. Moore gives us a number of interesting clinical notes made by Sir Theodore Mayerne on various patients of high rank, including James I, Charles I and his Queen. He also tells us of the work of Mayerne, Sydenham, and Glisson, and shows that it was by their practice and writings that the study of clinical medicine was established in Great Britain. In the fourth lecture he continues his subject down into the eighteenth century, and then gives a most interesting digression on the early history of medicine in Ireland and Scotland. We know of few lecturers who have condensed as much really valuable material into so small a space and, at the same time, have been able to tell their story in such an interesting manner. F. R. P.

A MANUAL OF OTOLOGY. By GORHAM BACON, A.B., M.D., Professor of Otology in the College of Physicians and Surgeons, Columbia University, New York, with an introductory chapter by CLARENCE JOHN BLAKE, M.D., Professor of Otology in Harvard University. Fifth edition; pp. 508; 147 illustrations and 12 plates. New York and Philadelphia: Lea & Febiger, 1909.

WITH each edition Bacon's *Otology* is not only increased in size, but, if possible, improved in its arrangement and contents. The book has long since been recognized as the representative American

manual of otology. To the present edition Dr. Bacon has added a number of new illustrations and a concise but excellent account of the operation of tonsillectomy and the submucous resection of the nasal septum. This edition, like each of the previous editions, shows every evidence of careful revision of the text on the part of the author. Every subject is brought thoroughly up to date. No better book could be recommended to the student or practitioner who wishes an authoritative presentation of the subject of otology. F. R. P.

ILLUSTRATIONS OF THE GROSS MORBID ANATOMY OF THE BRAIN IN THE INSANE. A SELECTION OF SEVENTY-FIVE PLATES SHOWING THE PATHOLOGICAL CONDITIONS FOUND IN POSTMORTEM EXAMINATIONS OF THE BRAIN IN MENTAL DISEASE. By I. W. BLACKBURN, M.D., Pathologist to the Government Hospital for the Insane, Washington, D. C.; Professor of Morbid Anatomy in the Medical Department of the University of Georgetown, and in the Department of Medicine of the George Washington University, Washington, D. C. Pp 154; 75 plates. Washington: Government Printing Office, 1908.

OUR knowledge of the gross morbid anatomy of the brain in the insane is by no means as complete as it should be, and Dr. Blackburn has done a real service in presenting this work, in which there are 75 excellent plates. The technical difficulties in preparing the photographs for such a work as this are many, and the author is to be congratulated for the excellent results obtained. No one who has not worked in neuropathology can appreciate the many difficulties which beset the preparation of brains for such a work as this, and it is indeed a pleasure to commend the good results obtained.

The collection of pathological specimens from which the photographs were made were selected from among 2350 autopsies, and the author has endeavored to give examples of most of the common changes in the adult insane. He has followed a pathological classification rather than a clinical one, and the specimens include brains from general arteriosclerosis with or without cerebral softening, hemorrhages, atrophy of the brain, meningo-encephalitis or paresis, hydrocephalic states, meningeal conditions, and brain tumors. As the author states, it is of course understood that the lesions represented in no sense are to be considered as showing the essential morbid anatomy of any form of mental disease except general paralysis and possibly senile dementia and arteriosclerotic dementia. In many instances the lesions were purely accidental and had nothing to do with the form of insanity. Opposite each plate is a brief statement of the name, age, and clinical diagnosis, with a more extended, but brief, discussion of the lesions. T. H. W.

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UNDER THE CHARGE OF

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Acute Addison's Disease.—STRAUB (*Deut. Arch. f. klin. Med.*, 1909, xcvii, 67) reports a case of Addison's disease, which is of importance as throwing light on the time relation between the onset of the pathological process in the adrenals and the beginning of clinical symptoms. This is the most acute case yet reported, the duration of the disease being only seventeen days. The onset was marked by severe abdominal pain and vomiting. There was, at times, watery diarrhœa. Ten days later reddish discoloration of the skin appeared over various points of pressure. These later assumed a more brown color. There was no pigmentation of the mucous membranes. The blood pressure remained 105 mm. Hg., until the day of the death, when it fell to 99 mm. The clinical diagnosis was malignant tumor of the lungs, pyloric stenosis, and tumor in the right lumbar region. The symptoms, pigmentation, asthenia, psychical disturbance, and sudden death also suggested Addison's disease. Autopsy showed scirrhous carcinoma of the pylorus with multiple metastases. Both adrenal glands were involved, but only to a very moderate degree. The most striking lesion of the adrenals was a general venous thrombosis, the apparent age of which corresponded well with the duration of the symptoms. Straub believes that the obstruction to venous outflow was the etiological factor in the case.

[There are a number of cases in literature in which destructive processes in the suprarenal capsules have resulted fatally, and in a considerably shorter period of time with symptoms closely similar to those described in this case. Indeed, a syndrome consisting particularly of sudden abdominal pain, vomiting, diarrhœa, tachycardia, asthenia, psychical disturbances, hypothermia, collapse, often similar to that

observed in peritonitis, and sudden death, has been described by Sergent and Bernard (*Compt. rend. soc. de biol.*, Paris, 1898, 24 sec.; L'insuffisance surrénale, Par., Masson, 1903, Collection Léanté), as characteristic of acute insufficiency of the adrenals. In the works referred to a number of interesting illustrative cases may be found. The striking feature in this case appears to be the rapid appearance of the pigmentation which, however, does not seem to have been especially characteristic.—W. S. T.]

Two New Tests for Albumin in the Urine.—Oguro (*Zeit. f. exp. Path. u. Therap.*, 1909, vii, 349) presents two new qualitative tests for albumin in the urine. Were it not for the fact that his tests are apparently specific as well as simple, he would hesitate to add to the already long list. Test I, with tincture of iodine and sodium bisulphate. Method of application: A few cubic centimeters (5 to 6) of the urine—which must, of course, be clear—is placed in a test-tube and acidified with a few drops of dilute acetic acid. About $\frac{1}{5}$ volume of tincture of iodine (10 per cent.) is now added, and the whole is well shaken. A dirty, dark brown precipitate results. A saturated solution (watery) of sodium bisulphate is next added drop by drop, shaking constantly, until the brownish fluid is decolorized. If the urine contains albumin, one sees a permanent whitish cloud or flocculent precipitate. If no albumin is present, the fluid remains clear after the addition of the sodium bisulphate, and shows only the original urinary color. With minimal quantities of albumin, the reaction becomes more evident on standing a few minutes. Test II, with decolorized tincture of iodine. Method of application: One decolorizes tincture of iodine with saturated watery solution of sodium bisulphate and filters. The filtrate is a clear, rather yellow fluid, which keeps well. On standing for some time, small, yellow crystals may be precipitated, without injury to the reagent. The urine, as in Test I, is acidified with dilute acetic acid. About $\frac{1}{3}$ volume of the reagent is added and the whole well shaken. If albumin is present, a cloud or a flocculent white precipitate forms. With traces of albumin the reaction may be delayed a few minutes. Normal urine never shows a cloud with these tests. For control Oguro has always employed the Heller-Spiegler heat, and the sulphosalicylic acid tests. In two years Oguro has never found a urine in which salts, alkaloids, or other non-albuminous substances led to confusion. The tests are sensitive to albumin in a dilution of 1 to 120,000.

Abdominal Palpatory Albuminuria.—Schreiber (*Deut. Archiv f. klin. Med.*, 1909, xcix, 1) has made an elaborate study of albuminuria resulting from certain manipulations in abdominal palpation, in which the aorta both above and below the renal arteries has been compressed and the effect of pressure on the vena cava has been noted. He finds, by the aid of measurements from bony landmarks and of skiagrams, that the renal vessels may be localized with great precision. Spontaneous albuminuria from abdominal palpation is very seldom seen. It certainly is not due to compression of the vena cava, but may easily arise from compression of certain parts of the aorta. Compres-

sion of the aorta at the point where the renal arteries are given off is easily accomplished in suitable cases and always leads to albuminuria. It is seldom the case that one can palpate the aorta above the origin of the renal arteries, but when possible, pressure here also causes albuminuria. In either case the albuminuria is more marked and persistent the more complete the compression and the longer it is maintained. Even an incomplete arterial compression of a few seconds may suffice to produce albuminuria. Arterial albuminurias appear quickly from slight changes in the aortic pressure and are generally of high albumin content. Pressure exerted on the aorta below the renal arteries causes no change in the urine. Compression of the vena cava above the renal veins leads to the development of albuminuria much more slowly, and the albumin appears in relatively small amount.

The Staining of Moist Preparations with Azure-eosin (Giemsa).—GIEMSA (*Deut. med. Woch.*, 1909, xxxv, 1751) has contributed a new staining method which should prove of special interest to those interested in tropical medicine. It is intended for the staining of moist smears and fresh tissue by means of his azure-eosin mixture, which gives the characteristic Romanowsky staining. The details of the method are as follows: (1) Fix the smears while still moist or the tissue in sublimate alcohol. (Concentrated watery $HgCl_2$, 2 parts; absolute alcohol, 1 part.) The cover glass is placed in the solution before it dries, with the specimen side down; later it is turned over. Fixation requires twelve to fourteen hours. (2) Wash quickly in water and then five to ten minutes in a solution of KI, 2 gm.; Lugol's solution, 3 c.c.; and distilled water, 100 c.c. (3) Wash in water very quickly and place in a 0.5 per cent. aqueous solution of sodium thiosulphate, by which the yellow staining of the iodine solution is completely removed. (4) Place in flowing water five minutes. (5) Stain with freshly prepared Giemsa solution one to twelve hours. After the first half hour the stain should be renewed. (6) Wash in water and carry through the following: (*a*) Acetone, 95 c.c.; xylol 5 c.c.; (*b*) acetone, 70 c.c.; xylol, 30 c.c.; (*c*) acetone, 30 c.c.; xylol, 70 c.c.; (*d*) xylol, pure. (7) Embed in cedar oil. The time in solutions (*a*), (*b*), and (*c*) depends on the differentiation desired. The method is especially valuable in the study of protozoa, such as malaria, infusoria, trypanosomes spirochetes, etc. Beautiful results are also obtained with tissue.

A Muscle Bundle Between the Superior Vena Cava and the His Bundle.—THOREL (*Münch. med. Woch.*, 1909, lvi, 2159) reports findings which will be of considerable importance in the physiology and pathology of the heart. By making serial sections and reconstructing a model, he has demonstrated, in two adult human hearts studied, that there is a continuous bundle of muscle connecting the superior vena cava with both the Keith-Flack nucleus and the Aschoff-Tawara nucleus. This bundle is readily distinguishable histologically, consisting of Purkinge cells. A detailed account will appear soon.

The Excretion of Uric Acid Injected Intramuscularly in Gouty Subjects.—Brugsch and Schittenhelm have given uric acid and purin bases to

gouty patients with purin-free food and have studied the elimination of uric acid in the urine and feces. As there was always the possibilty of bacterial decomposition in the intestines, BENCZUR (*Zeit. f. exp. Path. u. Therap.*, 1909, vii, 339), at the suggestion of Brugsch, injected a known quantity of uric acid intramuscularly to determine how much of it could be recovered. As the procedure is not without unpleasant consequences, such as marked local and constitutional symptoms, Benczur omitted controls on normal individuals, obtaining them from the literature. The work of others has shown that healthy persons excrete 50 to 99 per cent. of uric acid injected intramuscularly. Benczur repeated the experiment on a patient suffering with gout. He injected 0.5 gm. uric acid into the gluteal region; the patient had been on a purin-free diet for several days, and it was found that the average daily output of endogenous uric acid was 0.2101 gm. During the two days immediately following the injection 81.6 per cent. of that given had been excreted. Benczur believes it not unlikely that the increase was due in part to the destruction of leukocytes, because of the marked local reaction, together with fever and general malaise, which followed the reaction. The same occurred in the normal individuals reported in literature. The experiment shows that the gouty patient eliminated uric acid injected intramuscularly just as a healthy subject does. In other words, the renal excretion of uric acid in the gouty is apparently normal.

The Effect of Compression of the Superior Mesenteric Artery upon the Systemic Blood Pressure.—Arteriosclerosis of the splanchnic arteries, presumably on account of its action in setting up increased peripheral resistance to the flow of blood, and thus raising the systemic blood pressure, has long been accounted a cause of cardiac hypertrophy. LONGCOPE and MCCLINTOCK (*Univ. Penna. Med. Bull.*, 1909, xxii, 226) have studied this condition experimentally in dogs by noting the changes in blood pressure produced by compression of the superior mesenteric artery. In five minutes the vessel was compressed or ligated forty-three times, and in every instance a rise of blood pressure resulted. The average elevation of pressure varied from 4.5 mm. to 10.3 mm. The changes in arterial pressure seemed to vary in direct proportion to the amount of constriction. When the compression was of short duration the elevation of blood pressure continued until the experiments were stopped, but when the vessel was ligated for a longer period, the primary rise in pressure was, except in one instance, followed by a secondary fall to normal. Compression of the aorta at the level of the diaphragm produced a marked and rapid rise in blood pressure, but neither compression at the bifurcation nor ligation of one or both renal arteries resulted in any alteration in systemic pressure.

A Quantitative Index to Tuberculin Treatment.—The two factors of value in tuberculin treatment are toxin tolerance and reaction. Toxin tolerance is the object to be gained in acute cases which have become afebrile, and it is obtained by the use of doses small enough to avoid reactions. In chronic cases, and in certain others, which, after long

treatment, have come to a standstill, the productions of mild reactions are apparently beneficial. One difficulty in the therapeutic administration of tuberculin has hitherto been the impossibility of determining accurately the dosage, which in a given individual will, on the one hand, give the greatest stimulation without reaction, or, on the other hand, will produce a reaction of mild grade. Basing their work on experience with the cutaneous tuberculin test, WHITE, GRAHAM, and VON NORMAN (*Jour. Med. Research*, 1909, xxi, 225) have formulated a procedure to govern accurate dosage. They have found that a definite ratio exists between the amount of tuberculin applied cutaneously and that given subcutaneously for the production of local and constitutional reactions. Thus, one-fifteenth of the amount of O. T., which when applied to the skin produced the minimal cutaneous reaction (a local redness about 4 mm. in diameter) would, when given subcutaneously produce both local and constitutional reactions. One-thirtieth of the same amount subcutaneously would produce local without constitutional reaction, while one-fiftieth produces neither local nor constitutional reaction. Thus, by the use of a definite quantity of O. T. on the skin, it is possible to determine (1) the borderland of reaction and absence of reaction to tuberculin which will be the degree of tolerance to tuberculin of the patient, and (2) the dose of tuberculin necessary to give the grade of reaction desired. In their cutaneous tests, the authors used 0.01 c.c. of various percentages of O. T., and protected the point of application with a vaccine shield in order to allow complete absorption.

The Treatment of Pneumonia by Leukocytic Extract.—Continuing the work of Hiss, FLOYD and LUCAS (*Jour. Med. Research*, 1909, xxi, 223) have used extracts of leukocytes in the treatment of 41 cases of pneumonia. The leukocytes were obtained from the exudate produced by the injection of aleuronat into the pleural cavities of rabbits. While the general mortality of lobar pneumonia is given by Musser as 21 per cent., the mortality of this series was only 12.2 per cent. Of the 5 fatal cases, 2 were bronchopneumonia in children, 2 were complicated by cardiac lesions, and 1 was a man, aged seventy years. About 44 per cent. terminated on or before the sixth day of the disease. The most striking result of the treatment was a definite constitutional improvement, relief of labored respiration, and improvement of such symptoms as might be due to toxemia. The extract was administered subcutaneously in doses of 10 c.c. twice daily. In no instance did the treatment do any harm, but in three instances an urticarial eruption appeared after an interval of four to seven days. Following the beginning of inoculation there was a steady diminution in the number of leukocytes in the peripheral circulation. The evidence of effect on the process in the lungs was not distinct.

Aseptic Purulent Meningeal Exudates.—WIDAL (*Revue mens. de méd. interne et de thér.*, 1909, i, 1) has considered carefully that group of cases showing the signs of meningitis in which lumbar puncture gives a thick, purulent but sterile exudate. An exudate of this character was first described as occurring in syphilis, but has since been met with in la grippe, pneumonia, puerperal eclampsia, uremia, suppurative

otitis, after spinal cocainization, in mumps, and in meningeal conditions of unknown origin. The process may be a slow latent one, or it may begin with acute, alarming symptoms. On bacteriological examination of the spinal fluid, cultures, staining, and inoculations all prove it to be sterile. Especial stress is placed on the histology of the polynuclear cells present, for Widal asserts that the fact that these cells retain their normal structure is in itself evidence of the sterility of the fluid. For examination the sediment of the centrifugalized fluid is fixed on a slide and stained with hematin and eosin. In septic exudates the contour of the cells is indistinct, and both nucleus and protoplasm undergo marked changes. In sterile exudates the nucleus has a delicate texture, the protoplasm is perfectly homogeneous with fine granules, and the contour of the cell is distinct. The great importance of recognizing cases of meningitis with sterile exudate is that, in spite of what may appear to be a most unfavorable condition, the prognosis is excellent, for most cases result in complete recovery.

Experimental Transmission of Acute Poliomyelitis.—Flexner and Lewis (*Jour. Amer. Med. Assoc.*, 1909, liii, 1639) have issued a preliminary report of their experiments in the inoculation of monkeys with the material obtained from two cases dying of acute poliomyelitis. An emulsion in salt solution of the spinal cord from the children, and later emulsions of the spinal cord of previously inoculated monkeys, were introduced through a trephine opening in the skull. In each instance the inoculated animal became paralyzed after a somewhat variable period. Histological study of the spinal cords of the monkeys showed in every case lesions similar to those of poliomyelitis in man.

[It is difficult to overestimate the importance of this communication. The power of reproducing the disease in an indefinite series of animals may well prove to be the first step in the production of a curative or preventive serum.—W. S. T.]

Arteriosclerosis of the Pulmonary Artery.—While the lesser circulation is usually unaffected in cases of generalized arteriosclerosis, in certain cardiac conditions, and especially in mitral stenosis, the pulmonary vessels alone may show signs of degeneration. Lanbry and Parvu (*Tribune méd.*, 1909, xlii, 484) report the case of a girl, aged twenty years, who had never had any rheumatism or any other infectious disease, but who had suffered with cardiac symptoms for many years. The diagnosis of mitral stenosis was made, and was confirmed at autopsy when the mitral opening was found to be nearly occluded. The aorta and the smaller arteries of the general circulation were in a practically normal condition, but the pulmonary arteries showed thickening and sclerosis in their whole extent. Lanbry and Parvu agree with Vaquez and Giroux, who have reported a similar case, in believing that the underlying cause in the production of this localized arteriosclerosis is the hypertension resulting from the narrowing of the mitral orifices. They also consider that the frequent and profuse pulmonary hemorrhages which occurred in their patient were greatly facilitated by the diseased condition of the vessels.

SURGERY.

UNDER THE CHARGE OF

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Rupture of the Biceps of the Arm.—LEDDERHOSE (*Deut. Zeit. f. Chir.*, 1909, cl, 126) says that according to his observations, neither a pure traumatic rupture of the biceps nor a traumatic separation of the upper pole occurs. The dislocation of the outer belly outward, which has frequently been described and illustrated, occurs in most cases spontaneously. The position of the long head of the biceps and the resulting defect are caused by arthritis deformans of the shoulder-joint. It is an occupation deformity. In the overwhelming number of cases described in the literature as traumatic ruptures of the biceps, there already existed pathological changes in the biceps tendon, and the trauma acted as the exciting cause. The occurrence of an indirect, purely traumatic rupture of a biceps tendon, not already invaded by a diseased process, must be doubtful. The very widely accepted view that an indirect, traumatic rupture occurs generally at the upper juncture of muscle and tendon, is not well supported. It appears questionable whether an indirect, traumatic rupture occurs in this portion. A rupture of the distal tendonous portion of the biceps at its insertion into the radius or in the immediate neighborhood appears to be determined by a preceding pathological process. Wounds of various grades in the muscular portion from direct trauma, have been repeatedly observed. Whether tears of the muscle substance can occur from indirect trauma has not been shown satisfactorily by the literature of the subject. The conditions which have been described as herniæ of the biceps, are, almost without exception, cases of dislocation of the outer belly of the biceps.

The Surgery of the Heart.—SALOMONI (*Archiv. gén. de. chir.*, 1909, iv, 881) had previously collected and reported 134 cases of cardiorrhaphy. He now calls attention to some new facts concerning this operation. He approaches the heart through the intercostal space which is the seat of the external opening of the wound, enlarging the wound by scissors and disarticulating from the sternum one or two adjacent costal cartilages. For wounds of the base of the heart or of the right cavity he advises a transverse section of the sternum. By retraction, an opening 8 cm. wide can be obtained with this method. He counsels drainage of the pericardium after every cardiorrhaphy, when one is not sure of his asepsis. The reason for it is the same as for peritoneal drainage. The

serosa of the pericardium absorbs less than that of the peritoneum, and intrapericardial collections of blood are absorbed slowly. Of 58 cures, in 30 pericardial drainage had been practised. Pericardial effusion is frequent after cardiorrhaphy. It localizes itself posteriorly to the heart, and produces precordial oppression, anxiety, and weakness. The frequency of the pulse and cyanosis of the face appear only late. Up to the present time Salomoni has collected 158 cases of cardiorrhaphy. Of these, 59, or 37.33 per cent., were cured, and 99 died; 21 died before the end of the operation or soon after. There were 2 cases of double wound of the heart, and 1 case of gun-shot wound with the missile remaining in the ventricle. Some cases are irremediably mortal from simultaneous lesions of both cavities, valvular lesions, or lesions of the motor centres. Wounds of the heart through and through are not always fatal. In 5 such cases the posterior wound was unrecognized. Lesions of the coronary arteries are often fatal from arrest of the heart, cardiac degeneration, infarct, and aneurysm. Ligation of one of the branches of a coronary artery can be followed by a cure. The branches of the coronary arteries are not terminal, so that their successful ligature is possible. If the heart is arrested during cardiorrhaphy, light massage can make the heart beat anew. For the diagnosis of a cardiac wound, one should take into account, the seat of the wound, the symptoms of internal hemorrhage, increase of the cardiac dulness, the appearance of oppression, precordial distress, cyanosis, and rapidity of the pulse.

A Comparative Study of the Value of Internal Urethrotomy and of Divulsion.—Cimino (*Ann. d. mal. d. org. gén.-urin.*, 1909, ii, 1361) says that the supporters of each of these two operations defend their positions forcibly up to the present time. He studied the subject from the standpoints (1) of the lesions and histological changes produced from the time of the operations to the final results, and (2) the septic phenomena, local and general, occurring after each operation. As the work was done on animals, traumatic strictures alone were studied. He traumatized the urethras, on the same day and by the same method, of ten animals, of the same species, of the same weight, and with urethras of the same calibers. Although the work was done only on traumatic strictures, Cimino believes that the results can be legitimately applied to the gonorrhœal type. Internal urethrotomy produces, at the site of the stricture, a linear, longitudinal, and regular section, the depth of which is preëstablished. As the wound widens it is transformed into a triangular or rectangular space opening into the urethra. It cicatrizes on the surface with a thin layer of fibrous tissue under the epithelium. The lesion produced by urethrotomy is strictly localized, so that it affects the stricture tissue only at the line of section. Divulsion produces tears of variable importance, and may pass in all directions. Upon healing, these lesions produce numerous extensive and irregular cicatrices, which reproduce the original lesions. New deformed and capricious strictures are added to the original one. The general aspect of the divulsed urethra varies according to the time when one observes it, but it is always characteristic. Immediately after the operation it presents as a bursted hollow organ; 8 days later it appears as a torn and fringed canal. When the lesions have become definite, the urethra appears as a rigid pipe, or a canal the surface of which is re-

duced to shreds. Divulsion terminates in the total transformation of the stricture into a cicatricial ring, with some epithelial elements scattered in the homogeneous, compact, fibrous tissue. These are always found on the surface of the urethra and in the glandular cavities, but they present the phenomena of proliferation and degeneration. Internal urethrotomy is, therefore, superior to divulsion. The septic condition of the urethra does not exercise any influence upon the choice of one or the other of these operations, as neither guarantees against the development of infectious lesions, local or general.

The Operative Treatment of Ununited Fractures.—CREITE (*Deut. Zeit. f. Chir.*, 1909, cl, 267) reports observations on 30 cases of ununited fracture operated on in Braun's clinic. The most frequent cause of non-union (18 cases) was the interposition of soft tissues between the fragments. The tibia was involved in 28 cases, the femur in 1 and the humerus in 1. In 17 cases the fracture was simple and in 13 compound. The time of operation was from four to twenty-eight weeks after the accident. In most cases (18) Bier's passive hyperemia and percussion at the seat of fracture, had been tried for several weeks, without success. In 15 cases, the old Dieffenbach method was employed, the seat of fracture being freely exposed by a flap incision. Ivory pegs were introduced, one above and the other below, into holes drilled through the bone, and the pegs were cut off level with the surface of the bone. In some cases, one of the bones of the leg was fixed with the ivory peg, and the other with wire sutures. The course of the healing was undisturbed in all, the pegs healing in. In no case was it necessary to remove the pegs secondarily. The time necessary for union varied from five weeks to twenty-eight weeks, the average being eight and one-half weeks. In one case, in which a steel nail had been employed, union failed. In 14 cases the ends of the fragments were resected and sutured together. One of these died eleven days after the operation from sepsis. In this case, however, there had been a compound fracture of the leg, and there had been an acute osteomyelitis of the tibia for about fourteen years. Three and a half weeks after his admission to the clinic, the necrotic bone was removed and the ends of the bone sutured. In 2 cases no bony union took place. In one there had occurred a severe compound fracture, with a torn, soiled wound, followed by severe suppuration and destruction of the periosteum of the fragments. The wire suture led to the formation of a fistula, and later the suture was removed. In the second case there had been a compound fracture of the humerus, with the loss of a 7 cm. piece of the whole thickness of the bone. The remaining 11 cases left the clinic with union, but in some the healing had been troublesome, and in 4 cases the suture had to be removed later on account of fistulæ. As a result of these experiences the Dieffenbach method is given the preference over the resection method.

Resection of the Middle Portion of the Duodenum.—KAUSCH (*Zent. f. Chir.*, 1909, xxxvi, 1350) says that resection of the descending portion of the duodenum may become desirable for various causes. A frequent and probably the most important indication seems to be a carcinoma of the papilla of Vater. The operation most frequently done is by a

transduodenal or retroduodenal approach. After it is determined that the case is not one of gallstones, the tumor with the neighboring portion of the duodenum is excised, and provision made for the proper evacuation of the common bile duct and pancreatic duct. Körte's case lived three and three-quarters years after operation. Those of Halsted and William J. Mayo were both soon followed by recurrence. Kausch thinks this is one of the most favorable of cancers for removal, because it becomes recognizable early and when yet small, owing to the severe jaundice without colic which it causes, and which drives the patient to the surgeon for relief. It then lies in the wall of the duodenum, remains localized a long time, and does not metastasize until late. This portion of the intestine is easily removed, but the anastomosis of the gall and pancreatic ducts complicate the operation considerably. No severe operation should be done in the presence of severe jaundice. The gall and pancreatic ducts should not be introduced at the line of sutures in the divided bowel, as that would give an untrustworthy anastomosis. The operation should be performed in two stages. In the first, Kausch, upon opening the duodenum, found a bean-sized nodule exactly at the papilla of Vater, with no metastasis, no gallstones but the gall-bladder about the size of the fist. An anterior cholecystenterostomy was performed with a small Murphy button, about 50 cm. from the plica duodenojejunalis, and about 12 cm. lower an enteroanastomosis with a large Murphy button. Ten days after the operation the large, and three days later the small, button passed the rectum. The jaundice disappeared and the weight improved slightly. Sixty-seven days later the second operation was performed. Numerous adhesions lengthened the first part of the operation. The anastomoses made in the first operation were in good condition. The duodenum was isolated up to the pylorus, the head of the pancreas separated from it, and a posterior gastro-enterostomy was performed. The pyloric end of the stomach was closed blindly; the duodenum beginning above was shelled out, taking away with it a piece of the head of the pancreas the size of a walnut; the bile duct was ligated; the duct of the pancreas was cut open in the pancreatic tissue; and the duodenum divided somewhat above the junction of the descending and inferior portion. The remaining lower open end of the duodenum was sutured, hood-like, over the cut surface of the pancreas with catgut sutures. This area was covered over with omentum, a cigarette drain introduced, and the abdominal wound sutured. Twenty-one days after the operation the patient was well and had increased 2.5 kilograms in weight.

The Conservative Treatment of Severe Wounds of the Extremities Threatening Gangrene.—NOESSEKE (*Zentralbl. f. Chir.*, 1909, xxxvi, 1377) says that in severe wounds of the fingers, especially those from incised and contused wounds, we are often in doubt whether the remaining narrow and poorly nourished bridge of skin will permit the hanging part to live. The conservative treatment frequently fails. The cause of the gangrene is the deficient arterial supply and the retarded outflow of venous blood. The venous stasis is the most prominent symptom in these wounds, as in cases of frost-bite. High elevation with moist warm applications are usually employed to overcome the circulatory disturbances, and frequently fail. In several severe finger wounds,

in a case of frost-bite of both thumbs, and in a case with asphyxia threatening gangrene from Raynaud's disease, a broad incision was made to the bone anteriorly, beginning below the level of the nail and extending over the end of the finger. The success was astonishing. The wound was tamponed with gauze soaked with camphor oil to prevent adhesion of the wound surfaces. The hand, including the wounded finger, was then exposed by a suction apparatus to a negative pressure of about 12 to 15 cm. of mercury for eight to ten minutes. This was kept up for a week, and applied two or three times daily. In the beginning there escaped dark cyanotic blood, drop by drop. Later arterial blood welled forth, which daily increased in amount. This passive hyperemia treatment had been tried repeatedly in the case of Raynaud's disease, and had failed completely. The incision was, therefore, the chief cause of success. In the cases so treated the sensation returned in a few hours, and the wounded part lived and retained good function. Further observations must determine how valuable this method will prove to be in the involvement of larger portions of the limbs. It may prove of value in threatening or advancing gangrene of other origin, plastic operations, transplantation of organs, and for the improvement of the circulation through the sutured vessels.

The Role of Heart Massage in Surgery.—WHITE (*Surg., Gynec., and Obstet.*, 1909, ix, 388) says that heart massage is an established method of resuscitation, ten successful cases having been reported by ten operators. Heart failure is rarely primary in chloroform anesthesia. It is, therefore, essential that respiration be invoked by artificial means in conjunction with heart massage. Artificial respiration alone will not inaugurate heart contractions nor maintain blood pressure. The best results have been obtained by the subdiaphragmatic method. The most frequent indication for its use is chloroform narcosis with cessation of respiration and circulation. In other conditions of heart failure secondary to respiratory failure, and not dependent upon organic changes in the heart, the method is applicable. Further use of the method will widen its field of usefulness. The possibility of resuscitation bears a definite relation to the time that has elapsed between the cessation of the heart beat and massage. The briefer the interval the more rapid is the response to heart massage. White says that the entire question is unsettled, that the 50 cases tabulated is only an incentive to further research, that each additional case is of value, and that some time may yet elapse before we can adjust heart massage in proper accord with its surgical bearings.

Bone Sarcoma.—BUERGER (*Surg., Gynec., and Obstet.*, 1909, ix, 431) adduces the following facts from a careful study of twenty bone sarcomas: To the expansive type belong the phenomena of "ping-pong" or "egg-shell" crackle. Bone expansion is a feature of a majority of the bone sarcomas examined, and occurs in the shaft as well as in the extremities of the long bones. We should recognize the diffuse infiltrative variety as one which may remain latent until pathological fracture occurs; and should remember that normal bone contour is not compatible with the presence of intramedullary growths. Certain destructive types, causing fusiform enlargement of the part, and very frequently

involving the upper end of the fibula, are malignant tumors that soon penetrate into the soft parts. A combination of chronic osteoperiostitis with central sarcoma may occur. Calcification in the osteoid and chondroid tumors is a feature which may be of great value in diagnosis. Periosteal bone production is also to be utilized in diagnosis. Skiagrams are of great importance in the recognition of these tumors. We should look for the characteristic periosteal bone deposition and especially for dense shadows in the diaphysis as well as in the epiphysis, with a view to diagnosticating the sclerosing type of osteoid and chondroid sarcoma. The extensive calcification and the slow endosteal progress exhibited by certain types suggests that early diagnosis may be possible. To discover the presence of endosteal lesions before the more malignant extra-osteal masses have been developed should be a desideratum. Fine, radiographic bone detail is essential for an adequate interpretation of the pathological changes. A large tumor in the soft parts is no reliable measure of the extent of the bone destruction or the size of a central focus if such there be. Large tumors outside of the bone may be associated with a very slight lesion in the bone.

THERAPEUTICS.

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The Use of Atropine Sulphate and Atropine Methylbromide in Diabetes Mellitus.—RUDISCH (*Med. Record*, 1909, xxvi, 1093) has treated a number of cases of diabetes mellitus with the above salts of atropine. A carbohydrate-free diet was also given at the beginning of the treatment in conjunction with the atropine. His results were so satisfactory that he advises the use of these salts by other investigators. Rudisch sums up the action of atropine in this series as follows: (1) A reduction in the amount of sugar excreted; (2) an increase in carbohydrate tolerance. Under the first heading he says that it was uniformly observed that the glycosuria disappeared much more rapidly under this combined form of treatment than withthe customary antidiabetic treatment alone. He calls attention to the fact that while a strict carbohydrate-free diet will usually cause a marked diminution in sugar excretion, traces of sugar will still remain in the urine or appear from time to time. In these cases Rudisch found that the use of atropine in sufficient dosage invariably resulted in a complete suppression of the glycosuria. Interruption in the administration of the drug without change in the diet was followed in many of the cases by the reappearance of sugar in the urine. This glycosuria could always be made to disappear again by resuming the atropine. Rudisch believes that the influence of atropine in increasing

carbohydrate tolerance is manifested in two ways. He found that patients could tolerate much larger quantities of carbohydrates when atropine was admimistered. He also noticed that the tolerance for carbohydrates increased after the prolonged administration of atropine. He administered the atropine in the form of the methyl bromide and the sulphate. The former has the advantage of being much less toxic. but its effects are not so prompt as those of the sulphate. Its cost, moreover, limits its use. Rudisch advises that methyl bromide should be given to adults in the dosage of $\frac{2}{15}$ grain three times a day, gradually increasing this by $\frac{1}{15}$ grain until $\frac{8}{15}$ grain three times a day are being taken. In one case 3 grains were given daily over a short period with no other toxic effect than dryness of the throat. The initial dose of atropine sulphate should be $\frac{1}{150}$ grain three times a day, and that may be gradually increased to $\frac{1}{20}$ grain three times a day. Children require a dosage proportionate to their age. Rudisch observed no toxic effects from this dosage. When a marked dryness of the throat occurred the atropine was discontinued temporarily, or more often the dosage was not increased. No deleterious effect upon the general health was observed from the prolonged administration of these salts of atropine.

The Process of Cellulose and Hemicellulose Digestion in Man, and Their Food Value.—LOHRISCH (*Zeit. f. exper. Path. und Therap.*, 1909, v, 478), in an exhaustive article, concludes a number of previous observations concerning the digestion of the celluloses and hemicelluloses in man. He refutes the prevalent opinion that the cellulose group and the closely allied hemicelluloses are digested in the human intestine by bacterial fermentation. He cites much experimental evidence to support his view that the digestion of the celluloses and hemicelluloses occurs in the same way in man as that of the starches. Lohrisch's conclusions are as follows: (1) Cellulose and the hemicelluloses are closely related chemically. Certain individual chemical characteristics, however, serve to differentiate them. (2) They show no marked differences in their physiological behavior. (3) Man is able to digest 50 per cent. of cellulose and the hemicelluloses under normal conditions. Individuals with habitual constipation are able to digest from 70 to 80 per cent. (4) Man is able to digest larger quantities of the hemicelluloses than of cellulose. (5) The digestion of the hemicelluloses and cellulose occurs in the same way in man as the digestion of the starches; that is, they are converted in the intestines to their corresponding sugar. Their conversion and absorption, however, occur more slowly than is the case with the starches. The quantity absorded is completely burned up in the human body. Consequently, proteid and fat are saved from katabolism. Probably glycogen is also stored up in the tissues if an excess has been absorbed. Cellulose and the hemicelluloses are not split up into the volatile fatty acids in the small intestine. Probably only a small portion of the unabsorbed material is changed in the large intestine to the volatile fatty acids, and as such, re-absorbed. (6) Cellulose and the hemicelluloses are harmless substitutes for the ordinary easi y absorbable carbohydrates. The hemicelluloses are of practical worth as substitutes when ordinary carbohydrates are not well borne.

The Influence of Different Carbohydrates upon the Glycosuria in Diabetes.—WERBITZKI (*Zeit. f. exper. Path. und Ther.*, 1909, vi, 235) has tested in several diabetics the effect of different carbohydrates upon the excretion of sugar. He gave his patients a meat and fat diet for from three to five days in order to determine the grade of glycosuria on a non-carbohydrate diet. He then tried the effect of different carbohydrates upon the excretion of sugar, separating the carbohydrate periods by meat and fat periods. He used for this purpose bread, rice, buckwheat, milk, potatoes and oatmeal. Of these substances oatmeal by far seemed best adapted to supply the necessary carbohydrates for diabetics. The authors conclusions are as follows: (1) The different carbohydrate-containing substances exercise an entirely different influence upon the glycosuria of diabetics when these substances contain the carbohydrate in pure form; (2) oatmeal in large quantities causes in many cases of diabetes no increase in the glycosuria, therefore oatmeal has a special place among the carbohydrate containing foods; (3) this action seems to be specific in the case of oatmeal and possibly may be explained by a peculiar difference in the chemical composition of oatmeal compared to the other carbohydrates; (4) the oatmeal diet exercises in the majority of cases a favorable effect upon the glycosuria. At the same time the general condition improves and the subjective symptoms become less marked. Therefore, oatmeal is to be preferred to the other carbohydrate-containing substances in the treatment of diabetes; (5) finally, in order to secure the best results from the use of an oatmeal diet, Werbitzki believes that it is necessary to exclude all other carbohydrates from the diet.

The Treatment of Gastric Ulcer.—MAYERLE (*Arch. f. Verdauungskrank.*, 1909, xv, 337) reviews the various methods for the treatment of gastric ulcer, and reports his results in 71 cases treated by the Lenhartz method. His cases include 29 recent, bleeding gastric ulcers, 17 chronic, and 25 uncomplicated, acute cases; 65 per cent. were cured in a short time. A slower recovery without recurrence was noted in 11 per cent. of the cases, and with recurrence in 14 per cent. No benefit was obtained in 10 per cent. of the cases. There were a few cases in which the diet was not tolerated. Mayerle could detect no injurious effects, even when the diet was commenced immediately after the hemorrhage. He found that the Lenhartz diet occasionally seemed to increase the tendency to hyperchlorhydria. In these cases he advises an increase in the proportion of fat in the diet and, at the same time, a reduction in the proportion of albumin. In the chronic cases with reduced acidity, a diet with less albumin, a moderate amount of fat, and an increase in the carbohydrates seemed to give the best results.

Optic Atrophy from the Use of Atoxyl and Arsacetin.—PADERSTEIN (*Berl. klin. Woch.*, 1909, xxii, 1023) describes in detail a case of optic atrophy occurring as a result of injections of atoxyl. He also discusses 6 similar cases reported by different observers. Besides these cases with well-defined optic atrophy, Paderstein was able to find in the literature reports of 22 cases of severe disturbances of sight from the use of atoxyl. He could determine no relation between the size of the dose used and the severity of the disturbance of the sight. In the

typical cases the injury is manifest by a concentric diminution of the field of vision beginning on the nasal side, which finally leads to a diminution of central vision and often to complete blindness. The harmful effect of atoxyl extends to the nerve elements of the retina and consequently disturbances of color vision especially violet blindness, may be caused. Less often a narrowing of the retinal arteries is noted. Paderstein thinks that the poisonous action of atoxyl upon the visual apparatus is probably due to the aniline component. This may be true, since similar results are observed in aniline poisoning, but not in arsenical poisoning. He also says that it has not been actually determined that arsacetin is less dangerous than atoxyl, although this has often been asumed.

The Use of Phosphorus in Rachitis.—SCHABAD (*Zeit. f. klin. Med.*, 1909, lxviii, 94) reports the results of further studies of the effects of phosphorus on the metabolism in rachitis. In a previous paper he demonstrated that phosphorus, dissolved in cod-liver oil markedly increased the retention of calcium in rachitis. His present paper deals with the effect of the administration of cod-liver oil alone. His experiments showed that it increased the calcium retention but considerably less than when given with phosphorus. He also found that inorganic calcium, when given with phosphorus dissolved in cod-liver oil, was retained to a large extent, and the author, therefore, recommends these three remedies for the treatment of rachitis.

The Treatment of Obesity.—LAISSUS (*Jour. des Prac.*, 1909, xviii, 281), after a study of 200 cases of obesity, recommends as of primary importance a reduction in the amount of carbohydrates and fats ingested. If the patients complain of hunger during the first few days of treatment the allows them to eat fairly large quantities of fresh fruits and green vegetables. He advises frequent small meals with a minimum of salt, to lessen the appetite. Fluids should be restricted at meal times to one-half pint. Since the obese require a considerable amount of fluid, it should be given in the form of drinks one hour before, and three hours after meals. Laissus also advocates the various physical methods such as exercise, hydrotherapy, and massage. Exercise should not be excessive and taken regularly under specific directions. Hydrotherapy is given in the form of hot baths in running water, and the alternating hot and cold shower. Massage, to be beneficial, should be prolonged for some time, and the kneading process is preferable. He believes that drugs are of little use and that thyroidin is actually dangerous. He has found that some cases of obesity are benefited by the administration of a few drops of tincture of iodine in milk. Obesity associated with arteriosclerosis is often beneficially influenced by small doses of sodium iodide.

PEDIATRICS.

UNDER THE CHARGE OF

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Hemorrhagic Disease in the Newborn with Direct Transfusion.—The case reported by SWAIN, JACKSON, and MURPHY (*Boston Med. and Surg. Jour.*, 1909, clxi, 407) was that of an apparently normal newborn baby, whose paternal grandfather had died of pernicious anemia and one of its cousins of melæna neonatorum on the fourth day of life. The baby had nursed normally and had a good meconium movement before going to sleep. It woke up with a sharp cry, and the nurse found its clothes and bed saturated with a bloody stool, there being about 10 ounces of fluid blood. This was repeated several times, the blood being slightly thicker than normal blood. Fresh rabbit serum and diphtheria antitoxin did not check the bleeding, to the bloody stools being added bloody vomiting and hemorrhagic spots beneath the skin. The child was in extremis when direct transfusion from the father's radial artery to the child's internal saphenous vein was employed. The flow of blood was permitted to continue for five to six minutes, terminating in complete cessation of the hemorrhage. The child recovered perfectly. No cause can be given by the author, but the defect was probably not in the vessel walls, as is usually stated, but rather in the failure of the blood producing mechanism, which was remedied by some part of the normal blood which was introduced into the circulation.

Furunculosis and Acute Pemphigus Neonatorum.—REICHE (*Deut. med. Woch.*, May, 1909), in the staphylococcic skin infections of children, uses hot packs to promote free perspiration, thereby bringing the cocci near the skin surface, and then uses mercury baths to disinfect the skin. He tried this treatment with much success in furunculosis and pemphigus.

Glandular Fever.—J. E. BURNS (*Archiv. Int. Med.*, 1909, iv, 118) reports an epidemic of glandular fever (6 cases) occurring in the Children's Ward of the Union Protestant Infirmary, at Baltimore. The patients were from two and one-half to five years of age. He also reports 3 cases occurring in the family of one of the discharged patients, one arising within twenty-four hours of the child's reaching home. The Children's Ward had been isolated for two months before the appearance of the glandular fever, because of measles, scarlet fever, and diphtheria in Baltimore. In the case of the family infections referred to, the child had not been seen by any of its relatives for two and one-half months. All of the patients had a leukocytosis varying from 18,800 to 26,400, the small mononuclears being chiefly increased. The throats and tonsils of all the patients were injected, but showed

no exudate; the cultures showed Staphylococcus aureus. The cervical glands were enlarged on both sides simultaneously in 8 cases; in one case but one side suffered. The swelling and tenderness reached its maximum on the third day. The upper glands were especially affected. All the glands were hard and discrete; none suppurated. Stiffness of the neck disappeared with the tenderness. The portal of entrance was probably the tonsils and pharynx, the etiological organism Staphylococcus aureus. Nephritis was not noted in any case.

Fœtal Rickets.—J. R. CHARLES (*Brit. Jour. Children's Dis.*, 1909, vi, No. 67) reports a case of fœtal rickets and discusses the etiology. There was no history of diseased thyroid, tubercle, or syphilis in the family. The child was born with an enlarged head and with deformed bones, which were enlarged at the ends. She did not walk until three years old and the anterior fontanelle did not close until nearly the fourth year. About the fourth year examination showed the following condition: The head was square with marked frontal and parietal eminence; the teeth were badly shaped and carious; there was marked enlargement of the thyroid, both sides and isthmus. The radius and ulna on both sides were slightly bowed out, and the lower epiphyses were much enlarged. There was slight lateral curvature of the spine; and enlargement of the epiphyses of the lower ends of the femora and of the tibiæ and fibulæ. Both tibiæ were much bowed outward and forward. There was distinct beading of all the ribs at the costochondral junction; marked laxity of ligaments and fascia, marked flatfoot, and enlargement of the liver, below the edge of the ribs. The mental condition was bright.

Concerning the etiology of fœtal rickets Charles offers the suggestion that perversion of skeletal growth in intra-uterine life may be due to perversion of the thyroid function, since arrested conditions of skeletal growth are due to an arrested thyroid function, and removal of the thyroid in young animals arrests skeletal growth (Mackenzie). The beneficial effects of phosphorus in rickets may be exerted through the thyroid, since excretion of phosphorus is increased after administering thyroid gland and also in exophthalmic goitre. The good effects of phosphorus therapy in rickets, some claim, is due to improvement in calcium circulation, and the tetany of rickets is attributed to the poverty of calcium in the central nervous system. The thyroid is frequently enlarged during pregnancy, and Blair Bell states he found the blood calcium index low, in cases of hyperthyroidism, as in exophthalmic goitre. Therefore, Charles thinks that possibly the thyroid enlargement in this case is connected with the bony changes and that it is not present as an independent entity.

Glioma of the Spinal Cord.—GEORGE PEACOCKE (*Brit. Jour. Children's Dis.*, 1909, vi) reports the occurrence of glioma of the cord in a girl, aged eleven years, who had suffered no illness except typhoid fever in infancy. Five weeks before her death she suddenly complained of pain and stiffness in her neck, her head being bent over to the left side. This condition continued for one month, her general health remaining as usual. At the beginning of the fifth week she lost power to use her right hand. Malaise developed, and within the next few days severe

pain in the back of the neck and spine, and she could not bear to be moved. There was retention of urine, her right arm became paralyzed, and her right leg could be moved but slightly. Her temperature was at all times subnormal. On admission to the hospital at the end of the fifth week, the slightest movement caused her severe pain. Her face showed a marked cyanotic hue. Respirations were rapid, and a pneumonic area was found in the middle lobe of right lung. Paralysis of right arm and leg developed; sensation was present, both tactile and painful. Paralysis of the left arm and leg developed in a few hours, and death occurred from respiratory failure. Consciousness was retained throughout.

At autopsy there was found apparently a blood clot in the centre of the cord. On cross-section the blood discoloration was found to extend from the level of the thalamus scriptorum downward a distance of 11 cm. into the upper part of the cervical cord. Above, it lay posteriorly to the right side, and below terminated close to the central commissure in the postinternal column of the left side. Microscopic sections from the medulla and upper part of cord showed the structure to be glioma with small diffused hemorrhages. The outer portion was a network of neuroglia-cell processes, small, round cells, and blood-vessels, and inside this a zone of free blood. The small tumor lay in the postero-internal column of the cord, pressing on and distorting the normal portions of the white and gray matter. The crossed pyramidal tract in the right side was degenerated. Points of interest are: (1) The locality of tumor. Tumors of the spinal cord are relatively rare. The ratio to tumors of the brain is 1 to 13. (2) The age of the patient and the character of the tumor. Meningeal intradural spinal cord tumors preponderate over the medullary type, and of the latter tubercle is the commonest cause. (3) The duration of symptoms. This is usually about sixteen months.

OBSTETRICS.

UNDER THE CHARGE OF

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The Treatment of Retention of Pieces of Placenta with the Occurrence of Fever.—VEIT (*Zntrlbl. f. Gyn.*, 1909, No. 32)describes a case in which fever and hemorrhage continued after labor, and ceased when a piece of placenta was removed. Examination showed that streptococci were present and that the microörganisms found in the vagina were of the non-virulent order. He also describes the case of a patient who had fever after confinement, and who was treated by a physician by dilatation and curetting. Peritonitis developed, and the patient was brought to the clinic. On examination, hemolytic streptococci were present in the blood, and in the vaginal secretion hemolytic streptococci and the Bacillus coli communis. Extirpation of the uterus was

practised, and was followed shortly after by the death of the patient. On examination, peritonitis was present, hemolytic streptococci were found in abundance in the peritoneum, in the sinuses of the uterus, and throughout the circulation. Veit calls attention to the clinical rule that in the presence of actively virulent germs the physician should not disturb the uterus. In sapremia, and when the lower orders of bacteria only are found within the womb, decomposing material may be brought away to advantage. Microscopic and bacteriological examination of the secretions and fluids of the vagina gives valuable clinical information concerning the choice of operation. When the ordinary bacteria of putrescence are present, with fever and retention of placenta, the uterus should be emptied at once. When virulent streptococci are found in the vaginal secretion, but are not in the blood, the womb should not be disturbed. When the streptococci are not virulent, retained placental portions should be removed. When virulent bacteria are found in the blood and in the vaginal secretion, the prognosis for the patient is probably hopeless. The womb may be emptied or may be completely removed as a last resort.

Relation Between the Time of Rupture of the Fœtal Membranes and Lacerations of the Cervix Uteri.—COLYER (*Brit. Med. Jour.*, November 20, 1909) has studied in the General Lying-in Hospital of London 233 primiparous cases, in 164 of which vaginal examinations were made after labor. These examinations were made on the ninth or tenth day of the puerperal period, after thorough evacuation of the bowel and bladder. The conditions noted were the height of the fundus uteri above the pubes, the position of the uterus and the presence or absence of flexion, and the condition of the cervix, especially regarding the presence of lacerations. These were divided into three degrees: (1) Those extending less than half way up the vaginal cervix; (2) those reaching half way; (3) those extending to or beyond the junction of the vagina and cervix. In addition, the condition of the bases of the broad ligaments was studied to determine whether thickening of these tissues was present and to what extent. The character and quantity of the lochial discharge were also noted. In addition to these points, Colyer also sought to determine the relation between quality and quantity of the lochia, and the degree of uterine involution, the relation between the lacerations of the cervix and the condition of the involution, and also the relation between the cervical lacerations and thickening of the broad ligaments.

He was not able to establish a definite relation between the character of the lochia and the degree of involution present. Opinions differed as to a relation between the thickening in the broad ligaments and the degree to which the cervix was torn. Colyer was surprised to find that he could establish no relation between the lacerations of the cervix and the degree of uterine involution present.

He was able, however, to establish a relationship between the degree of dilatation of the os at the time when the membranes rupture, and the degree of lacerations of the cervix occurring during labor.

Five per cent. more severe lacerations occurred in cases, in which the cervix being thought by obstetricians to be dilated, the membranes were ruptured, than were observed in those cases in which the mem-

branes ruptured spontaneously and the cervix was subsequently found to be fully dilated. In cases in which the os was thought to be almost fully dilated, and the membranes were ruptured, deep lacerations occurred in 45 per cent. In those in which the os was not larger than a dollar, but 12.5 per cent. showed deep lacerations; but in every case in primiparous patients, in which the membranes were ruptured artificially, some laceration occurred.

An effort was made to consider the influence of the weight of the child and the diameters of the fœtal head upon the occurrence of cervical lacerations, but it could not be established that a definite relation exists between the two.

He tabulates 164 cases, the average age of the patient being 23.17 years. In these, slight lacerations occurred on the right side in 49.39 per cent., upon the left side in 46.93 per cent. of cases. Moderate lacerations occurred upon the right side in 15.24 per cent., and on the left side in 17.07 per cent. of cases. Deep lacerations occurred on the right side in 6.09 per cent., and on the left side in 12.18 per cent. of cases.

Where the membrane ruptured spontaneously with the os fully dilated, there were 33 cases, the average age being 21.16 years. Of these, there were slight lacerations on the right side in 48.48 per cent. and the same percentage on the left side. There were moderate lacerations on the right side in 3.03 per cent., and upon the left side in 21.21 per cent. of cases. Deep lacerations upon the right side were found in 6.06 per cent., and upon the left side in 9.09 per cent. of cases. Where the membranes were ruptured artificially there were 46 cases, the average age of which was 22.8 years. These had slight lacerations on the right side in 54.34 per cent. of cases, and upon the left side in 41.32 per cent. There were moderate lacerations on the right side in 19.56 per cent., and upon the left side in 36.95 per cent. of cases. There were deep lacerations upon the right side in 6.52 per cent., and upon the left in 15.21 per cent. of cases.

Where the os was almost fully dilated and the cases had rupture of the membranes either spontaneously or artificially produced, there were 11 cases, the average age being 23.52 years. Of these, there were slight lacerations on the right side in 36.36 per cent., and on the left in 27.27 per cent. of cases. There were moderate lacerations on the right side in 36.36 per cent., and on the left in 18.18 per cent. of cases. There were deep lacerations upon the right side in 9.09 per cent. and on the left side in 45.45 per cent. of cases. Where the os was not larger than a dollar, the cases numbered 6, the average age being 21.5 years. These had slight lacerations upon the right side in 50 per cent., and on the left side in 75 per cent.; moderate tear on the right side in 25 per cent., on the left in 12.5 per cent.; deep tear upon the left side in 12.5 per cent. of cases.

The practical conclusion of this research is that artificial dilatation and premature rupture of the membranes should be avoided whenever possible in the conduct of labor. It is much better to allow spontaneous dilatation to occur, and to interfere promptly in the second stage of labor, than to complete dilatation artificially by the premature rupture of the membranes.

The Position of the Patient during the Puerperal Period.—A contribution to the literature of the puerperal period, criticizing the proposition to allow puerperal patients to get up early, is made by HICKS (*Brit. Med. Jour.*, November 20, 1909). He believes that women, as a rule, do not want to get up after labor much before the expiration of two weeks, and that women among the poorer classes commonly complain of their hardship in being obliged to resume the upright posture. Hicks believes that rest is indicated to secure through involution of the entire genital tract, and also to encourage the successful establishment and performance of lactation. He is of the opinion that rest, good food, and a happy state of mind will do more to prevent prolapse of the abdominal and pelvic viscera than the few days exercise which the patient will obtain by rising early.

Hicks does not believe that the assumption of the upright posture has any essential influence in the development of septic infection. He believes that the recumbent posture is favorable for drainage, and that straining from respiratory efforts and coughing will dislodge any clots which will accumulate in the upper portion of the vagina. He also does not believe that the upright posture helps to prevent backward displacements. In his view the pelvic diaphragm is overstretched, often torn and relaxed during labor, and the recumbent posture is necessary for its complete involution. If it remains without involution, he believes that the weight of the uterus and other abdominal viscera is thrown upon the pelvic floor, which increases venous engorgement and tends to produce retroversion, prolapse, and congestion. He believes that there is abundant clinical evidence that the uterus not only maintains its normal position more easily with the patient recumbent, but that a retroverted or prolapsed pregnant uterus will not, in nine cases out often, resume a normal position if the patient is not kept in a recumbent position. He further believes that the recumbent posture favors the relief of venous engorgement of the pelvic organs, and allows the supports of the uterus to resume their proper function.

GYNECOLOGY.

UNDER THE CHARGE OF

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The Pathology of the Red Degeneration of Uterine Myomas.—SMITH and SHAW (*Jour. Obst. and Gyn. Brit. Emp.*, 1909, xv, 225) after a careful study of five specimens together with the cases connected with them, have decided that: (1) The chief change found in "red degeneration" of fibroids of the uterus consists in thrombosis of the bloodvessels. (2) This thrombosis and red coloration may commence at the periphery of the tumor. (3) The tumors are also in a state of degeneration,

as evidenced by a homogeneous material separating the muscle bundles in many places. (4) The tumors contain fat and fat crystals, probably derived from the breaking up of the muscle bundles. (5) The tumors are liable to become infected by septic organisms and so give rise to acute toxic symptoms. (6) Pregnancy is probably a predisposing factor in the causation of this condition.

Combination of Pfannenstiel's Transverse Incision and Shortening of the Round Ligaments in Operative Treatment of Complicated Retroflexio Uteri.—RICHARD WERTH (*Zentralbl. f. Gynäk.*, 1909, xxxiii, 477) combines the transverse incision of Pfannenstiel extending well beyond the lateral borders of the recti with shortening and suture of the round ligaments in the inguinal canal opened subfascially by loosening the aponeurosis of the externus muscle. The incision should be made close to the symphysis, thus avoiding the necessity of extensive loosening of the aponeurosis of the external oblique at the inferior wound margin. The incision should be carried to within 2 or 3 cm. of Poupart's ligament. Werth makes the incision immediately above the inguinal canal, as it facilitates orientation and affords additional protection against possible future hernia.

The Operative Treatment of Extensive Cystocele and Uterine Prolapse.—WATKINS (*Surg., Gyn.*, and *Obst.*, 1909, viii, 471), in a paper read before the American Gynecological Society, described an operation he had devised and performed 68 times for extensive prolapse of the uterus and bladder. It is done as follows: The anterior vaginal wall is severed from the uterus by a transverse incision, and through this opening the bladder is separated from the vagina, and the vaginal wall then divided in the median line. The bladder is next separated from the uterus and the peritoneum opened. The fundus uteri is now brought in contact with the anterior end of the opening in the vaginal wall and sutured in that position. The flaps of the vaginal wall are sutured to the uterus and to each other. But one failure is known among the 68 patients. Various modifications are made if the procreative period is not passed and if the uterus is thought to be too large.

Epithelioma of the Uterus After the Menopause; Early Hysterectomy.—REYMOND (*An. de gyn. et d'obst.*, 1909, xxxvi, 115) reported the cases with the accompanying specimens of 7 cases, in each of which the patient had had discharges of blood from the uterus some time after the menopause. One of them was a young woman, from whom the uterine appendages had been removed some time before. In every one of them palpation and specular examination had failed to find a lesion. In 4 of the 7 the lesion was in the body of the organ, in 1 in the isthmus, and in 2 in the cervical canal. Cancer was present in each. In one recurrence was noted at the end of four years.

Skin Metastases in Cancer of the Uterus.—HEINRICH OFFERGELD (*Monatsschr. f. Geburtsh. u. Gynäk.*, 1909, xxix, 871), in reviewing the literature, compiled 27 cases of skin metastases in uterine cancer. A careful study of the cases showed that metastases of the skin and mammæ

are rare in uterine cancer, and that they usually appear in advanced carcinoma. They occur most commonly in the region of the umbilicus and the mammæ. They are of hematogenous, probably of lymphogenous, origin. Aside from other potent factors, the cause of occurrence of skin metastases may be attributed to the close relationship of the surface epithelium of the uterus to the epithelium of the body surface. Skin metastases, as a rule, do not give rise to clinical symptoms. Carcinoma of the distal portions of the urogenital apparatus, which usually arise through retrograde lymphogenous transport, although they may occasionally arise by way of the blood channels, occupy a special reservation as regards frequency and origin. They occur preferably after corpus carcinoma, but they also occur in carcinoma of the cervix, and in the earlier stages even. Their presence, however, does not indicate that the case is inoperable.

Atresia of the Vagina with Hematometra, Hematosalpinx, and Hematovarium.—A. BROTHERS (*The Post-Graduate, 25th Anniversary Volume*, 1908), collected 164 cases of vaginal atresia and its consequent blood accumulations occurring during the past twenty years. Spontaneous rupture or evacuation occurred in 10 of primary blood retentions and in one secondary blood retention. Probably none of them was associated with hematosalpinx. When the last mentioned condition existed a considerable mortality rate has been present. Of 19 cases of this sort, 4 died of or shortly after operation by the abdominal route. In 10 cases the operation was successfully performed by the vaginal route.

Ureteral Fistulas as Sequels of Pelvic Operations.—In quite an exhaustive paper (*Surg., Gyn., and Obst.*, 1909, viii, 479) SAMPSON discusses ureteral fistula following pelvic operations, again emphasizing the importance of retaining the sheath of the ureter and of avoidance of injury to the blood supply of that duct. Reference is made to the changed relations of the ureters and uterus that are produced by displacements of the latter, either during or independent of surgical operations on these structures. Particularly is attention requested to such etiological factors in this respect as lateral displacement of the cervix uteri, the presence of appendages involved in inflammatory masses, and intraligamentary tumors. It is a notable fact that Sampson does not recommend the employment of the ureteral catheter or bougie as a prophylactic procedure. Sampson's advice regarding nephrectomy for ureteral fistula in which renal infection has ascended from a ureteral fistula is sound and indirectly is a strong argument for early surgical treatment of such fistulæ.

Necrosis of Fibromyoma of the Gravid Uterus as an Etiological Factor in Occlusion of the Intestinal Tract.—SPERÁNSKY-BACHMETEW (*Zentralbl. f. Gynäk.*, 1909, xxxiii, 553) reports a case of intestinal occlusion caused by necrosis of a fibromyoma of a pregnant uterus in a primipara, who presented the typical symptoms of loss of patency of the intestinal canal. Artificial interruption of pregnancy was not followed by improvement. Celiotomy was done. A pediculated uterine tumor was found beneath

the transverse colon; it was adherent to the great omentum; the latter was ligated off and separated. The adhesions to the sigmoid flexure were separated and the tumor removed by a wedge-shaped incision into the uterus. Uninterrupted recovery followed. The tumor was found to be a fibromyoma that had undergone hyaline degeneration and necrosis at the point where it had come in contact with the intestine. The growing uterus drew up the tumor with the adherent intestine, causing the short mesentery to exert an opposite or downward traction; constipation increased the meteorism, while prolapse of the descending colon augmented torsion.

Thrombophlebitis with Peroneal Neuritis and Paralysis Following Supravaginal Hysterectomy.—R. PETERSON (*Surg., Gyn., and Obst.*, 1909, viii, 517) reports a case of this kind which is employed as a basis for discussion. The peroneal palsy is attributed to either trauma or pressure upon the lumbosacral cord. The latter may be caused by an inflammatory process, and this often may arise from thrombosis; and if this process be considerable at the crossing of the left internal iliac vein and the lumbosacral cord, peroneal neuritis may result.

Experimental Studies of Postoperative Peritoneal Adhesions.—G. GELLHORN (*Surg., Gyn., and Obst.*, 1909, viii, 505) considers the problem of postoperative peritoneal adhesions from the standpoint of treatment resolves itself into two captions, viz., prevention of their formation and prevention of their again forming if separated. Under the first heading Gellhorn states the most rigid asepsis possible should be employed, raw surfaces and pedicle stumps should be covered by peritoneum or grafts of omentum, and the *en masse* ligature abandoned. Dry air contact should be avoided by moist asepsis and rapidity employed if possible. Avoidance of excessive manipulation of the peritoneum and proper bowel preparation and posture are considered important desiderata. Gellhorn emphasizes the necessity for careful replacement of the abdominal contents after intra-abdominal work, pouring hot salt solution on them at the time, and the early use of the high enema during the first twelve hours after the end of the operation, in conjunction with catharsis. In the consideration of preëxisting adhesions Gellhorn groups the subjects into: (1) Those adhesions formed from ectopic pregancy, (2) those from peritonitis, and (3) those from former operations. Gellhorn insists the first group leaves no lasting adhesions, and that in the two other groups permanent adhesions result. Reference is made to the experiments made by others before Gellhorn describes his experiments with lanolin, which were not productive of favorable results.

New Method of Shortening the Round Ligaments in Retroversion of the Uterus.—J. JERIE (*Zentralbl. f. Gynäk.*, 1909, xxxiii, 686) reports a new method of shortening of the round ligaments which he employed successfully in several cases of retroverted uterus. His method, in brief, consists of an incision in the linea alba 7 cm. in length, careful inspection of the uterus and adnexa, and eventual breaking up of adhesions or operation, if necessary, for the removal of diseased adnexa. The round ligament is grasped with artery forceps, 6 to 10 cm. removed from the

horn of the uterus, and an incision 1 cm. in length is made in the anterior fold of the broad ligament at a distance of 2 cm. from the ligamentum rotundum. Through this incision a small artery forceps is introduced between the two folds of the broad ligament, grasping the round ligament, which is drawn out after having been freed from the surrounding connective tissue. The artery forceps first applied to the round ligament is now removed. The uterus is next grasped by the hand or bullet forceps and held while the upper muscular layers of the anterior aspect of the uterine cornu are undermined for a width of about 1 cm. with a narrow, two-edged knife, thus creating a canal, into which an artery forceps is then introduced. The isolated loop of round ligament is grasped by this forceps and drawn through the canal until it becomes visible on the mesial end of the canal, where it is fastened with a strong catgut button suture, transfixing the undermined piece of muscle, the round ligament, and the uterine wall proper. In addition a catgut button suture is placed at each end of the muscle bridge encompassing the uterine wall, one arm of the loop of round ligament, and the undermined muscular bridge. The peritoneum over the round ligaments will usually approach the muscle bridge and cover the loop of the round ligament completely. At times a small catgut suture may be necessary, however. The other side is operated upon in the same manner. The shortened round ligament is re-implanted into the uterine muscle itself at almost the same site of the original attachment, and the uterus remains in the small pelvis in correct position.

OPHTHALMOLOGY.

UNDER THE CHARGE OF

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Spirochæta Pallida in Syphilitic Eye Lesions.—CORBUS and HARRIS (*Ophthal. Rec.*, June ,1909, 294) have examined some 200 cases of specific lesions primary and secondary. They conclude that Spirochæta pallida is present in all syphilitic lesions, including those of the eye. In chancres and mucus patches the diagnosis should be made by the demonstration of the spirochete. All other lesions of the eye of syphilitic origin may be diagnosticated by means of the Wassermann test, as may also ocular lesions depending upon pathological changes in the nervous system of syphilitic origin. The same test should be applied in cases of suspected syphilitic origin. The Wassermann test depends upon the discovery of Bordet and Gengou, that bacteria or their extracts will unite with their corresponding antibodies by means of complement and fix it. (Complement is present in all sera. What it is, is not definitely known. It may be conveniently obtained from the blood of guinea-pigs.)

Acoin.—BRUNETIERE (*Clin. ophtal.*, July 10, 1909, 326) recommends subconjunctival and intramuscular injections in 1 per cent solution. The analgesic effect, although inferior to that of cocaine, is much more prolonged and entirely free from risk. Acoin is quite unstable and forms insoluble precipitates with most medicaments in solution; such chemical alterations diminish the analgesic properties of the drug; hence, to obtain the maximum effect in subconjunctival and intramuscular injections, it is advisable to inject first the solution of acoin, followed after an interval of one or two minutes by the medicament desired. Acoin may also be employed dissolved in oil, but this vehicle does not appear to be superior to aqueous solutions.

Normal Flora of the Rabbit's Conjunctiva.—TCHIRKOWSKY (*Annal. d'oculist*, April, 1909, 291) finds that the flora of the normal conjunctival sac of the rabbit presents a great variety of forms, and differs from that of man by the rarity of bacilli in aggregation. Both aërobic and anaërobic forms are present, among which some are of undoubted pathogenic effect upon the eye (Bacillus perfringens). The pathogenic power of the microbes which occur there most frequently is, however, inconsiderable; it is only under particularly favoring conditions, especially by the introduction of large numbers into the vitreous body, that the germs develop rapidly and entail destructive consequences to the organ.

The Etiology of Refractive Anomalies and Emmetropia.—STRAUB (*Zeit. f. Augenheilk.*, 1909, xxii, 236) observes that, in view of its overwhelming frequency, emmetropia has been assumed to be the normal refraction. But when the fact is taken into consideration that the eyes of the newborn are mostly hyperopic, while emmetropia, notwithstanding decided variations in the structure of individual eyes, is attained with great exactness in the adult and that only a minority of emmetropes become myopic during adolescence, one must assume some mechanism which guides the increase in the refraction of the newborn that emmetropia shall result, and which shall govern the eyes having arrived at emmetropia so that the majority shall not become myopic. Straub terms this mechanism "emmetropization." Emmetropization assumes that length of axis and lenticular refraction shall be so related that emmetropia shall result. Of these two factors, the lenticular refraction is the predominant. If the shape of the lens was brought about by two antagonistic muscles, the explanation would be apparent. Clonic contraction of the muscles would then cause positive and negative accommodation, while tonic contraction of the antagonists would determine the shape of the lens in repose. The tone of the ciliary muscle can only increase the refraction, not diminish it. The intra-ocular tension tends to give the eye a spherical form. The circular groove between the cornea and sclera opposes this tendency. The most elastic tissue would be unable to withstand such continuous pressure permanently. Muscle alone can offer constant resistance, and this is furnished by the circular portion of the ciliary muscle. It is the cause of the groove. The intra-ocular tension is the antagonist required; it is this which tends to smooth out the curve in consequence of which also the lens is flattened and the refraction diminished; the ciliary muscle by its tonic contraction

opposes such flattening and is the force which determines adaptation for distance. Such tonic contraction leads in the developing eye to permanence of structure of the form of the ciliary muscle, so that the length of the muscle which was in the beginning a dynamical factor becomes static. A slight degree of tone persists in the majority of eyes. An important practical question relating to the development of myopia arises in connection with these views. In such eyes also which have departed from emmetropia the *nisus* to adaptation for distance had also been active, but it has been overcome, the axis has increased in length. If the optical condition of emmetropia has been restored by fully correcting glasses, the mind has been given renewed opportunity to put in play the mechanism of emmetropization so that a psychic factor is the principal role in the efficacy of full correction. The emmetropia thus furnished will only be permanant in cases in which the subject manifests a desire to see clearly at a distance. If such desire is not present, the correcting glasses will not prevent the myopia from progressing. Loss of tone of the ciliary muscle diminishes the resisting power of the ocular walls and permits enlargement of the myopic eye. Full correction increases the power of the ciliary muscle in that it stimulates the accommodation.

Malignant Growths of the Frontal Sinus.—In reporting a case of this rare affection, SNEGIREFF (*Klin. Monatsbl. f. Augenheilk.*, 1909, 622) insists that there is no early symptom which differentiates a malignant growth from other affections of the frontal sinus, such as empyema or polyp. Prominence of its wall with consequent displacement of the eyeball and double vision, impairment of the sight, and pain are symptoms common to different conditions. The diagnosis cannot be made with certainty so long as the posterior wall is still intact, the meninges uninvolved, the growth limited to its original seat, etc.

Treatment of Strabismus by Operation upon the Non-squinting Eye.—BETTREMIEUX (*Annal. d'oculist*, 1909, 53) again urges tenotomy of the non-squinting eye. He argues that the fixing eye, by reason of the synergy of the lateral movements, can only maintain its proper position by exaggerating the deviation of its congener; after a moderate tenotomy of its internus, it readily conserves the correct position but this is only possible on condition that its congener does the same. He thinks that if Donder's theory is correct, operation upon the non-squinting eye is logical.

The Inner Pole Magnet.—MELLINGER (*Archiv. d'ophtal.*, 1909, 193) objects to the giant magnets usually employed, that the lines of force are too strongly divergent, tending as they do to join the opposite pole, so that the foreign body within the eye which must be magnetized by these same lines of force, is only affected by a small part of them—a disadvantage the more marked in proportion as the foreign body is lodged deeper within the eyeball. To compensate this loss, the transverse section of the iron bar may be augmented, but such increase in size interferes with facility of manipulation. In order to diminish this loss, Mellinger has had constructed a large solenoid with several hundred windings of wire of such size that the head may be placed

at its centre; upon the passage of an electric current through this a homogeneous magnetic field is produced the greatest density of which lies at the bisection of the axes of the solenoid. Here the lines of force are nearly parallel to the axis. Bits of iron brought to this spot are at once magnetized to saturation. When an iron rod is brought within the influence of the magnet, it as well as the foreign body within the eye becomes magnetic; the degree of magnetization is proportionate to the size of the rod, so that the effect can be graduated by varying the size of the latter, and too rapid issue of the foreign body may be avoided. By the employment of urrents of varying intensities, the operator has complete control of the attractive force he wishes to use.

PATHOLOGY AND BACTERIOLOGY.

UNDER THE CHARGE OF

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The Pathogenesis of Pernicious Anemia.—GRAFE and RÖHMER (*Deut. Archiv f. klin. Med.*, 1909, xcvi, 397) endeavored to isolate a hemolytic substance from the stools of patients suffering with ulceration of the intestines. They studied the stools from this point of view from 106 cases, all but 11 of which showed some gastro-intestinal lesion. A hemolytic substance was most constantly found in the stools of patients suffering with tuberculous enteritis (10 out of 11 cases), while normal cases gave practically negative results. In catarrhal jaundice, in liver diseases, and in cholecystitis positive findings were obtained in all 6 cases. In typhoid fever 113 experiments were done, 26 of which were positive in 45 experiments in the fastidium of the disease, 9 positive in 32 toward the close of the attack (Stadium decrementi), and 8 were positive in 36 experiments during convalescence. Grafe and Röhmer believe that the hemolytic substance appears in the stools whenever there is a disturbance of fat absorption, and they consider it necessary to exclude diarrhœic and fatty stools in order to determine by this method anything in regard to the state of the intestines. They do not consider, however, their results sufficiently established to be of any diagnostic importance, but they hope to determine how much ulceration is necessary to produce the lipoid hemolytic substance.

Application of the Deviation-of-Complement Test to the Detection of Albuminous Substances in the Urine.—C. H. WILSON (*Jour. Path. and Bact.*, 1909, xiii, 484) has found that very minute quantities of albumin may be detected in the urine by means of the deviation-of-complement

test. For antigen he has used the serum of rabbits which had been immunized against human blood serum. When albuminous urines were diluted to such a point that they no longer gave a reaction with heat and acetic acid or with nitric acid, they still yielded positive results by the complement-deviation test; while in many instances albumin could be detected by this method in diluted urine when it could not be demonstrated by the ordinary chemical tests. The deviating power of the urine is not affected either by filtration through a Berkefeld filter or by dialysis. The antibody of the urine was, moreover, found to reside entirely in the serum albumin and serum globulin, and after the removal of the substances from the urine the remaining fluid no longer had the property of an antibody. Wilson believes that by this method one may detect minute quantities of albumin in the urine, which cannot be demonstrated by any other means. The experiments show further that the albumin which occurs in the urine in nephritis and other conditions is native albumin, and not, as has been suggested by some observers, a proteid constitutent of the food which has passed unaltered. Most of the conclusions in regard to this so-called alimentary albuminuria have been drawn from experiments made by means of the precipitin reaction; and it was claimed by Ascoli in particular that egg albumin after ingestion could be found in the blood serum and in the urine. That albuminuria may occur after eating large quantities of raw eggs is well known, but recently Wells has shown by means of the anaphylaxis reaction that the albuminuria in such cases is due to the presence of true serum albumin. Guinea-pigs sensitized with urine from four healthy persons with experimental albuminuria, produced by eating raw eggs, and with the urine from two cases of nephritis, reacted typically and severely to subsequent injections of human ascitic fluid and not at all to egg white or egg albumin.

Recent Investigations upon Trypanosomiasis.—EHRLICH (*Arch. f. Schiff's-und. Tropen-hyg.*, 1909, xiii, 91) sums up the most recent investigations upon trypanosomiasis, which have been made in his labortory. One of the obstacles encountered in the therapeutic use of certain drugs in experimental trypanosomiasis is the gradual immunization of the parasite against the drug. By treating animals infected with trypanosomes repeatedly with certain preparations of arsenic it has been possible to obtain a variety of trypanosomes which is proof against that particular drug. This acquired property is retained through many generations, as many as 400 in one instance, and over a period of four years. The development of this arsenic-proof variety of parasite takes place, according to Ehrlich, in the following manner: The parasites contain, as do all other cells, certain chemical receptors, which Ehrlich terms chemoceptors and which have a specific affinity for the arsenic radical. By the union of these receptors with the arsenic radical the toxic effect of the drug upon the parasite is possible. By repeated injections of arsenic this receptor becomes saturated and can no longer bind the drug. Not only can arsenic-proof varieties be obtained, but a variety which is refractory to immune serum. The production of this immunity is, however, somewhat different from that just described. It has also been possible to cultivate through many generations in animals parasites which show a fairly specific resistance to other substances

besides arsenic. Parasites made proof against pyronin, however, are also proof against the arsenic preparations. This demonstration is of great practical value. Experiments upon the method by which the arsenic preparations cure an animal infected with trypanosomes go to show that the drug does not destroy the parasites but renders them incapable of reproduction. It was surprising to find that when arsenic-proof varieties were treated in vitro with weak solution of arsenic preparations their motility was stopped in three to seven minutes, whereas the ordinary varieties remain active for fifty minutes. This observation led to the discovery through other experiments that one portion of the parasites, that which is intimately connected with the motility, is readily susceptible to arsenic, while the substratum, which is connected with reproduction, is hyposensitive to arsenic preparations.

Among the arsenic preparations that have been used, it has been found by WENDELSTADT (*Berl. klin. Woch.*, 1908, No. 51) and ROEHL (*Zeit. f. Immunitätsforschung und exp. Therapie*, 1909, i, 1) that arsenophenylglycin is the most powerful against the parasite and least toxic to the host. Mice and guinea-pigs in the last stages of infections have been cured by a single dose. Moreover, this drug has proved more effective against the varieties proof against other forms of arsenic than any other preparation. The drug must be preserved *in vacuo*, for on exposure to air it rapidly oxidizes to form a highly toxic product. It has great advantages over atoxyl, arsacetin, and orsudan. The drug has already been used in Africa and double doses of 0.75 and 1 gram have been given without ill effects to the patient. Arsenophenylglycin may be made even more effective in animals by administering at the same time trypanosan by the mouth. Most brilliant results have thus been obtained in experimental trypanosomiasis, and the outlook for a similar therapy in man is most hopeful.

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